



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> C07D 307/62, A61K 31/34, C07D 307/91, 405/06, 417/06, 405/12, 413/12	<b>A1</b>	<b>(11) International Publication Number:</b> WO 98/07714 <b>(43) International Publication Date:</b> 26 February 1998 (26.02.98)
<b>(21) International Application Number:</b> PCT/US97/14878 <b>(22) International Filing Date:</b> 22 August 1997 (22.08.97)  <b>(30) Priority Data:</b> 60/024,440 22 August 1996 (22.08.96) US 60/024,586 22 August 1996 (22.08.96) US 08/915,099 20 August 1997 (20.08.97) US  <b>(71) Applicant:</b> OXIS INTERNATIONAL, INC. [US/US]; Suite 317, 6040 North Cutter Circle, Portland, OR 97217-3935 (US).  <b>(72) Inventors:</b> HOPPER, Allen, T.; 166 Jordan Circle, Somerset, NJ 08873 (US). ZIEMNIAK, John, A.; 715 Evans Road, Gwynedd Valley, PA 19437 (US). JOHNSON, Robert, E.; 270 Richard Way, Collegeville, PA 19426 (US).  <b>(74) Agents:</b> RENDA, Barbara, L. et al.; Klauber & Jackson, 411 Hackensack Avenue, Hackensack, NJ 07601 (US).		<b>(81) Designated States:</b> AU, CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> 5-SUBSTITUTED AND 5,5-DISUBSTITUTED-3,4-DIHYDROXY-2(5H)-FURANONES AND METHODS OF USE THEREFOR  <b>(57) Abstract</b>  The present invention relates to synthetic methods for the production of both optically active and racemic 5,5-disubstituted-3,4-dihydroxy-2(5H)-furanones; 5-[(4-aryl)-3-butynyl]-3,4-dihydroxy-2(5H)-furanones; 5-(2-arylthio)ethyl-3,4-dihydroxy-2(5H)-furanones; and 5-(2-aryloxy)ethyl-3,4-dihydroxy-2(5H)-furanones. This invention further relates to the use of the above mentioned compounds as anti-inflammatory agents through their action as mixed inhibitors of lipid peroxidation, 5-lipoxygenase, cyclooxygenase-1 and cyclooxygenase-2. The invention further relates to the use of such compounds in the treatment of chronic inflammatory disorders such as asthma, rheumatoid arthritis, inflammatory bowel diseases, atherosclerosis, acute respiratory distress syndrome, and central nervous system disorders such as Alzheimer's and Parkinson's diseases wherein reactive oxygen species and inflammatory mediators are contributing deleterious factors.		

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**5-SUBSTITUTED AND 5,5-DISUBSTITUTED-3,4-DIHYDROXY-2(5H)-  
FURANONES AND METHODS OF USE THEREFOR**

This Application claims priority from Provisional Applications Serial Nos. 60/024,440 and 60/024,586 both filed on August 22, 1996.

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**FIELD OF THE INVENTION**

The present invention relates generally to 5-substituted and 5,5-disubstituted-3,4-dihydroxy-2(5H)-furanones, methods of preparation therefor, and methods for their use.

**BACKGROUND OF THE INVENTION**

- 10 The *aci*-reductone 4-(4-chlorophenyl)-2-hydroxytetronic acid compound (CHTA) possesses antilipidemic and antiaggregatory properties which differ from those of the classical phenoxyacetic acids as has been disclosed in Witiak *et al.*, J. Med. Chem., 1988, 31:1434-1445 and Kamanna *et al.*, Lipids, 1989, 24:25-32. Although unsubstituted-, 2-alkyl- and 2-acyltetronic acids are frequently found in nature, the
- 15 2-hydroxy substituted tetronic acid redox system is found only in vitamin C and its closely related relatives (isoascorbic acid, erythroascorbic acid) and derivatives, and the macrolide antibiotic, chlorothricin.

- The antiaggregatory activities of 2-hydroxytetronic acid *aci*-reductone compound (CHTA) are of interest since blood platelets are involved in the genesis of
- 20 atherosclerosis. 2-Hydroxytetronic acid *aci*-reductones inhibit collagen-induced human platelet aggregation and secretion of [<sup>14</sup>C]-serotonin in a concentration-dependent manner at equivalent doses, as reported in Witiak *et al.*, J. Med. Chem., 1982, 25:90-93. The CHTA compound inhibits platelet function by a similar mechanism, involving arachidonic acid release. Redox analogues, such as 2-
- 25 hydroxytetronic acid, function as antioxidants in membranes or interfere with free radical processes involved in the biosynthetic elaboration of cyclic prostaglandin

endoperoxides (PGG<sub>2</sub> and PGH<sub>2</sub>), and, subsequently, thromboxane A<sub>2</sub> from arachidonic acid.

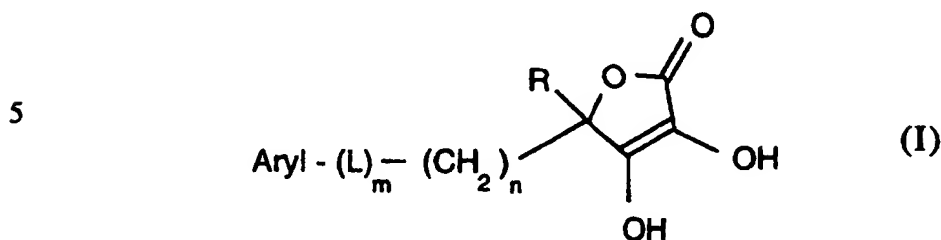
The development of dual antioxidant-arachidonic acid (AA) metabolism inhibitors may provide added benefits over existing drugs for the treatment of diseases associated with oxidative stress and inflammation. Numerous conditions including asthma, rheumatoid arthritis, irritable bowel disease (IBD), adult respiratory distress syndrome (ARDS), atherosclerosis, ischemia/reperfusion injury, restenosis, neurodegenerative disorders and initiation and promotion of carcinogenesis correlate with abnormally high levels of reactive oxygen species (ROS). Antioxidant-based therapies including both natural antioxidants (*e.g.*, vitamin E, vitamin C and SOD), and synthetic antioxidants (*e.g.*, 4-aryl-2-hydroxytetronic acids<sup>1</sup>, 2-*O*-alkyl ascorbic acids, probucol and tirilazad mesylate) have been, or are currently being, investigated for the treatment of a number of these conditions.

Previously, the *S*-arachidonic acid *aci*-reductone analog (*S*)-3, 4-dihydroxy-5 [(all *Z*)-3, 6, 9, 12-octadecatraynyl]-2 (5H)-furanone, was identified as a stereoselective and potent arachidonic acid metabolic inhibitor. This compound inhibits both PGE<sub>2</sub> and LTB<sub>4</sub> production in stimulated macrophages (IC<sub>50</sub> = 20 μM) and blocks AA-induced platelet aggregation (AAIPA) with an IC<sub>50</sub> < 10 μM. Dual cyclooxygenase (COX) and lipoxygenase (LO) activity could be important in preventing substrate shunting in the arachidonic acid cascade. Although this compound demonstrates an encouraging biological profile, both its instability and labored synthesis render this compound less than satisfactory as a therapeutic agent.

Thus, there exists a need for new therapeutic agents which exhibit activity as antioxidants and arachidonic acid metabolism inhibitors. It is to this aim that the present invention is directed.

#### SUMMARY OF THE INVENTION

The present invention relates to 5-substituted and  
5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones of the general formula I

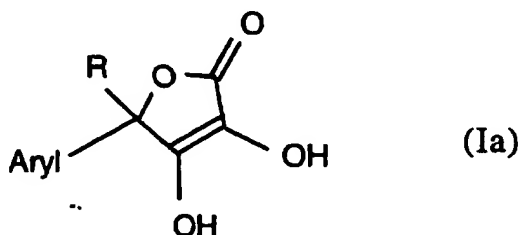


wherein R is hydrogen, phenyl or lower alkyl; L is a linker moiety selected from the  
10 group consisting of oxygen, sulfur, nitrogen, acetylene, a cis or trans carbon-carbon  
double bond, an ester, carbonate, urea, amide and carbamate; m is 0 or 1; n is 0 to 4;  
Aryl is a mono-substituted or unsubstituted aryl group; with the *proviso* that when R is  
hydrogen, then either m or n is not zero, and the pharmaceutically acceptable salts  
thereof.

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In various preferred embodiments of the present invention, these compounds are  
represented by four structural subclasses of compounds. Thus, in one preferred  
embodiment, the compounds are 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones of  
the structural formula Ia

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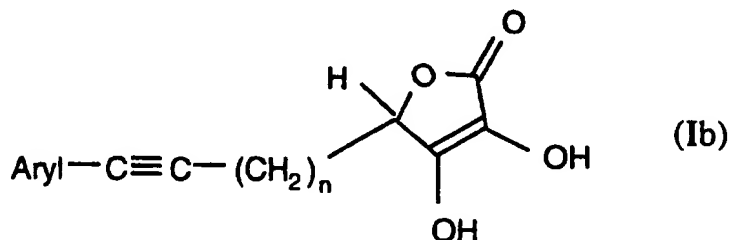
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wherein R and Aryl are as hereinbefore defined. Most preferably, in the compounds of  
formula (Ia), R is a methyl, 1-propyl or 2-methylpropyl group; and Aryl is a phenyl, or  
substituted phenyl, such as 1, 1'-biphenyl, 4-chlorophenyl or 2-methylpropylphenyl  
group.

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In a second preferred embodiment, the compounds are 5-(aryl  
alkynyl)-3,4-dihydroxy-2(5*H*)-furanones of the structural formula Ib

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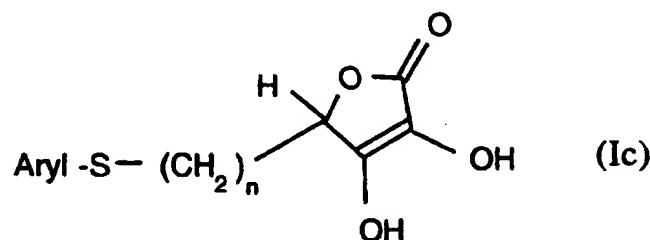
wherein  $n$  and Aryl are as hereinbefore defined. Most preferably, in the compounds of formula 1b,  $n$  is 2 and Aryl is naphthyl or a substituted phenyl such as 2-methylphenyl, 2-hexenyl phenyl, 2-phenylthiomethylphenyl or pentylthiomethyl phenyl.

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In a third preferred embodiment, the compounds are

5-(arythio)alkyl-3,4-dihydroxy-2(5*H*)-furanones of the structural formula Ic

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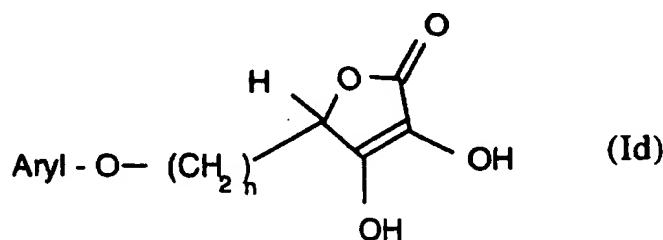
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wherein  $n$  and Aryl are as hereinbefore defined. Most preferably, in the compounds of Formula Ic,  $n$  is 2 and the Aryl substituent is naphthyl or 4, 5-diphenylisoxazole.

In a fourth preferred embodiment, the compounds are

5-(aryloxy)alkyl-3,4-dihydroxy-2(5*H*)-furanones of the structural formula Id

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wherein  $n$  and Aryl are as hereinbefore defined. Most preferably, in the compounds of formula Id,  $n$  is 2 and Aryl is a substituted phenyl or heteroaryl compound such as 1,12 biphenyl-4 yl, 4-phenoxyphenyl, flavonyl, dibenzofuranyl, quinoliny and naphthyl.

30

The racemic 5,5-disubstituted analogs of formula Ia are prepared by reacting an ethyl benzoylformate with a Grignard reagent and trapping the intermediate alkoxide anion with benzyloxyacetyl chloride, and subsequently adding lithium diisopropylamide to generate the corresponding 3-benzyloxy-5,5-disubstituted-4-hydroxy-2(5*H*)-furanones. Cleavage of the benzyl group by hydrogenolysis provides racemic 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones of formula Ia.

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The enantiomerically pure 5,5-disubstituted analogs of formula Ia are synthesized by reacting ethyl benzoylformate with a Grignard reagent, followed by ester saponification and resolution of the resultant 2-aryl-2-substituted-2-hydroxy acid by crystallizing with a suitable optically pure chiral amine to provide the optically pure compounds with non-racemisable stereocenters. Acid esterification, acylation of the hydroxyl group with benzyloxyacetyl chloride, LDA-induced intramolecular Claisen cyclization and reductive cleavage of the benzyl protecting group generates the 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones of formula Ia having high enantiomeric purity.

10 The 5-(aryl alkynyl)-3,4-dihydroxy-2(5*H*)-furanones of formula Ib are synthesized in a convergent manner by coupling 5-(alkynyl)-3,4-dihydroxy-2(5*H*)-furanone with aryl iodides by employing a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub>. The starting material, 5-(alkynyl)-3,4-dihydroxy-2(5*H*)-furanone, is synthesized in four steps. For instance, intermolecular Claisen reaction between  $\alpha$ -trimethylsilyloxy- $\gamma$ -butyrolactone and ethyl benzyloxyacetate yields 3-benzyloxy-4-hydroxy-5-(2-hydroxyethyl)-2(5*H*)-furanone. Iodination (I<sub>2</sub>, PPh<sub>3</sub>, imidazole), subsequent iodo displacement with lithium acetylide, and benzyl group cleavage yields, for instance, the 5-(3-butynyl)-3,4-dihydroxy-2(5*H*)-furanone coupling precursor.

The 5-(arylthio)alkyl-3,4-dihydroxy-2(5*H*)-furanones of formula Ic are produced by reacting a 3,4-dihydroxy-5-(iodoalkyl)-2(5*H*)-furanone with the lithium salt of a substituted arylthiol. The starting material, 3,4-dihydroxy-5-(2-iodoalkyl)-2(5*H*)-furanone is produced by benzyl group cleavage of 3-benzyloxy-4-hydroxy-5-(2-iodoalkyl)-2(5*H*)-furanone.

The 5-(aryloxy)alkyl-3,4-dihydroxy-2(5*H*)-furanones of formula Id are prepared by coupling 3,4-dibenzyloxy-5-(hydroxyalkyl)-2(5*H*)-furanone with an appropriately substituted phenol according to the Mitsunobu reaction. Subsequent benzyl group

cleavage by hydrogenation yields the desired 5-(aryloxy) alkyl-3, 4-dihydroxy-2(5H)-furanone.

### DETAILED DESCRIPTION OF THE INVENTION

5 As used herein, the term "alkenyl" means an organic, alkanyl group containing one or more double bonds and which can optionally be substituted by one or more halogen, lower alkanyl, alkoxy, aromatic or heteroaromatic groups. Examples of unsubstituted alkenyl groups include those such as 3-butenyl, 3- or 4-pentenyl, and the like. In a similar fashion, the term "alkynyl" refers to an organic, alkanyl group containing one  
10 or more triple bonds, of which 3-butyne, 3- or 4-pentyne and the like are representative.

The term "substituted or unsubstituted aryl", as utilized herein, means an organic, aromatic group which can be unsubstituted or substituted by one or more lower alkyl, lower alkenyl, lower alkenynyl, loweralkylthio, loweralkylsulfonyl,  
15 loweralkylsulfonylamino, aromatic or heteroaromatic groups. Examples of unsubstituted aryl groups include phenyl, pyridyl, thiophenyl, furyl, pyrrolyl and the like. Examples of substituted aryl groups include those such as alkyl-substituted aryl, *e.g.*, tolyl, 3-methylpyridyl, 2,3-dimethylphenyl, 4-ethylphenyl, 4-isobutylphenyl; alkoxy-substituted aryl, *e.g.*, 4-methoxyphenyl; loweralkylthio or loweralkylsulfonyl-  
20 substituted aryl, *e.g.*, 1-propylthiophenyl, 1-pentylsulfonylphenyl, lower alkenyl substituted phenyl, *e.g.*, 4-(2-(2Z-hexenyl)] phenyl and aryl-substituted aryl, *e.g.*, 1,1'-biphenyl and naphthyl. Complex aryl groups such as those derived from flavone, dibenzofuran, 1,8-naphthalimide, 1,8-naphtholsulfonamide, quinoline, 4,5-diphenyl-2-thio-1, 3-isoxazole, and naphthalenethiol can also be utilized as substituent groups.  
25 Particularly preferred are compounds wherein a 2- or 2,3-disubstitution pattern (relative to the alkenenyl or alkynenyl group) is present.

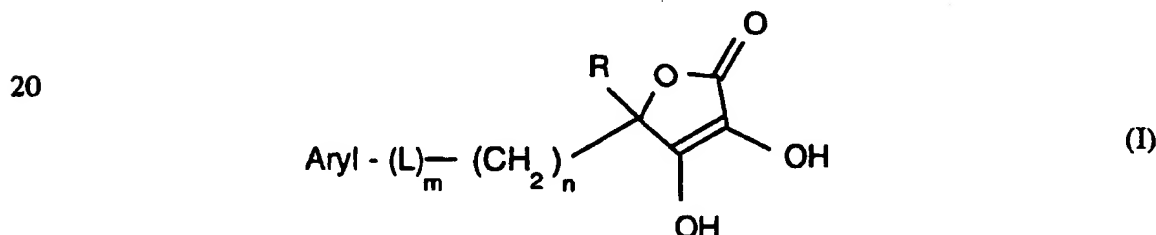


As used herein, the term lower "alkyl" means straight- or branched-chain saturated aliphatic hydrocarbon groups preferably containing 1-6 carbon atoms. Representative of such groups are methyl, ethyl, isopropyl, isobutyl, butyl, pentyl, hexyl and the like.

- 5 The term "alkoxy" means a lower alkyl group attached to the remainder of the molecule by oxygen. Examples of alkoxy include methoxy, ethoxy, propoxy, isopropoxy and the like.

- 10 The compounds of formula I can be formed as mixtures of enantiomers, as well as cis/trans isomers, due to the asymmetric carbon atoms of the ring structure and the double bonds present in the substituents. The present invention contemplates the use of both the individual isomers, as well as the racemic or cis/trans mixtures or both.

- 15 The present invention relates to 5-substituted-and 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanones of the general formula,



- 25 wherein R is hydrogen, phenyl, or a lower alkyl; L is a linker moiety selected from the group consisting of oxygen, sulfur, nitrogen, acetylene, a *cis* or *trans* carbon-carbon double bond, an ester, carbonate, urea, amide and carbamate; m is 0 or 1, n is 0 to 4, Aryl is a substituted or unsubstituted aryl group; with the *proviso* that when R is hydrogen, then either m or n is not zero; and the pharmaceutically acceptable salts  
30 thereof.

In general, the compounds of formula I wherein m and n are zero are prepared by:

- a) reacting a benzoylformate of the formula,

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wherein Alk is a lower alkyl group, Aryl is as hereinbefore defined with an organometallic reagent RMX wherein M is a group I or group II metal, X is a halogen, and R is as hereinbefore defined, to form an intermediate alkoxide of the formula,

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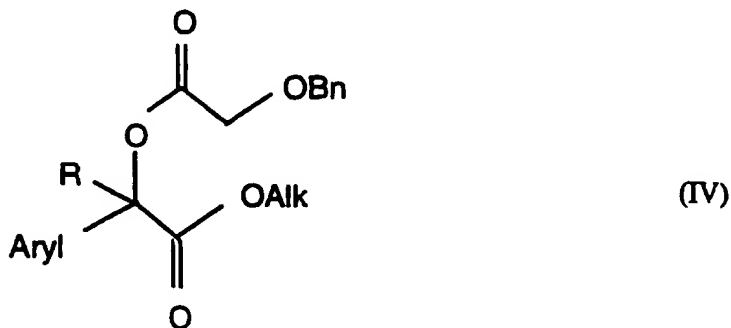


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wherein Aryl, R, M, Alk and X are as hereinbefore defined. The intermediate alkoxide is treated with a benzyloxyacetyl chloride, wherein Bn is a protecting group such as benzyl or a substituted derivative thereof, to provide an intermediate diester of the formula,

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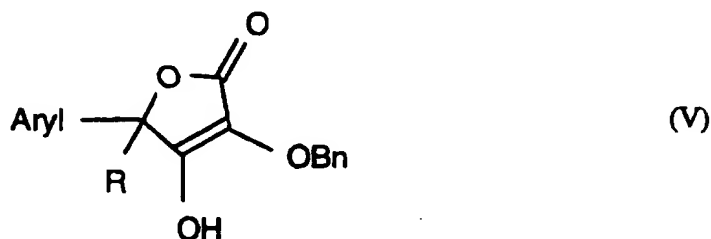
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wherein Aryl, R and Alk are as hereinbefore defined;

(b) Intramolecular Claisen cyclization of the diester of formula IV to the tetronic acid of the formula,

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wherein Aryl, R and Bn are as hereinbefore defined; and

15 (c) cleaving the benzyl protecting group of formula V by catalytic hydrogenation to yield the desired 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanone of the general formula I wherein Aryl and R are as hereinbefore defined, and m and n are 0.

Step (a) of the instant process utilizes as starting material, the appropriate benzoyl formate of the formula II wherein Aryl and Alk are as hereinbefore defined  
20 which can be purchased through commercial suppliers, or, if not commercially available, synthesized according to literature procedures. Benzoylformates are prepared by mixing an aryl compound, alkyl oxalylchloride and  $AlCl_3$  (or suitable Lewis acid) in a 1.0/1.1/1.1 mixture in 1,2-dichloroethane (or suitable solvent) at 0\_ to 10\_C with vigorous stirring and subsequently stirring the reaction mixture at  
25 25\_C for 24 hours according to the method of Kuchar et al., *Coll. Czech. Chem. Commun.*, 49: 122-136 (1984).

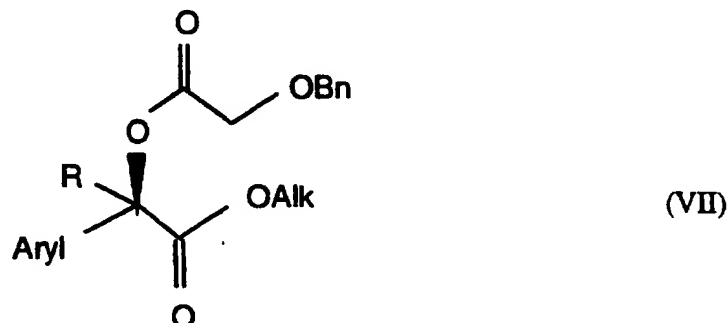
A process for the synthesis of enantiomerically pure analogs of the formula I wherein m and n are both zero comprises:

30 (a) reacting an optically pure 2-hydroxyester of the formula

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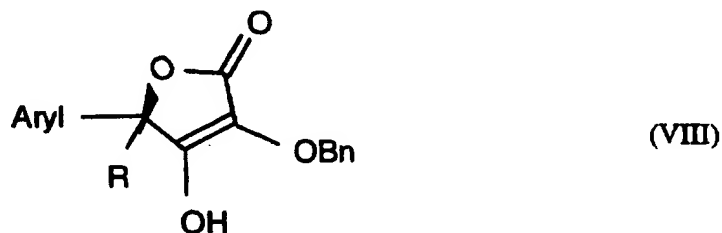


wherein Aryl, R and Alk are as hereinbefore defined with a benzyloxyacetyl chloride, wherein Bn is as hereinbefore defined, to provide an intermediate diester of the formula,



wherein Aryl, R, Bn, Alk and R are as hereinbefore defined;

- 15 (b) Intramolecular Claisen cyclization of the diester of formula VII to the tetronic acid of the formula,



wherein Aryl, R and Bn are as hereinbefore defined; and

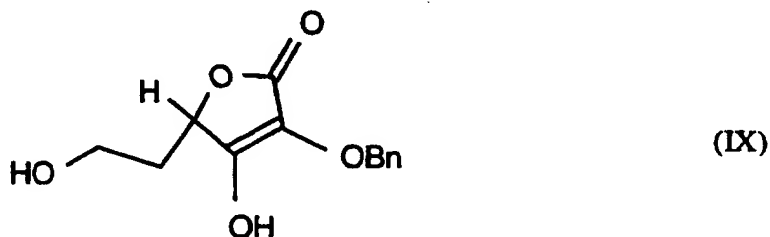
- 30 (c) cleaving the benzyl protecting group of formula VIII by catalytic hydrogenation to yield the desired optically pure 5,5-disubstituted-3,4-dihydroxy-2(5*H*)-furanone of the general formula I wherein Aryl and R are as hereinbefore defined, and m and n are both zero.

- 35 Step (a) of this process utilizes as starting material, an optically pure 2-hydroxyester of the formula VI, wherein Aryl, R and Alk are as hereinbefore defined, which can be purchased through commercial suppliers or, if not commercially available, synthesized according to literature procedures. Reaction of a benzoylformate with an organometallic reagent RMX, wherein R, M, and X are as hereinbefore defined, produces racemic 2-hydroxyesters of the formula VI, wherein aryl, R and Alk are as hereinbefore defined. Ester saponification with, for example, 1.0M NaOH, resolution with a:

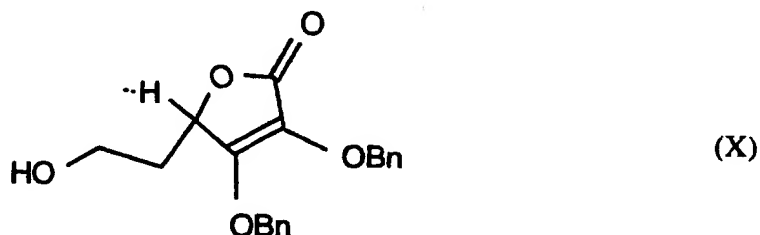
optically pure amine base using the method of Saigo et al., *Bull. Chem. Soc. Jpn.*, 55: 1188-1190 (1982) and esterification of the acid with, for example an ethereal solution of  $\text{CH}_2\text{N}_2$ , provides optically pure 2-hydroxyesters of the formula VI.

- 5 A process for the synthesis of analogs of formula I wherein R is hydrogen, Aryl is as hereinbefore defined, m is 1 n = 2, and L is an oxygen, ester, N-sulfonamide or N-imide linkage comprises:

(a) reacting a 3-benzyloxy-4-hydroxy-5-(2-hydroxyethyl)-2(5*H*)-furanone of the formula,



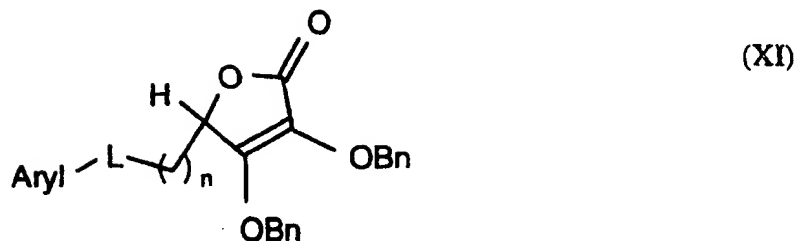
- wherein Bn is as hereinbefore defined with one equivalent of BnBr and one equivalent of triethylamine in THF for 5 hours at 65°C to provide 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone of the formula,
- 20



- 30 wherein Bn is as hereinbefore defined;

(b) reacting the 3,4-dibenzyloxy-2(5*H*)-furanone of the formula X with an aryl alcohol (i.e. phenol), carboxylic acid, sulfonamide, or phthalimide, wherein aryl is as hereinbefore defined, under Mitsunobu conditions to provide 3,4-dibenzyloxy-2(5*H*)-furanones of the formula,

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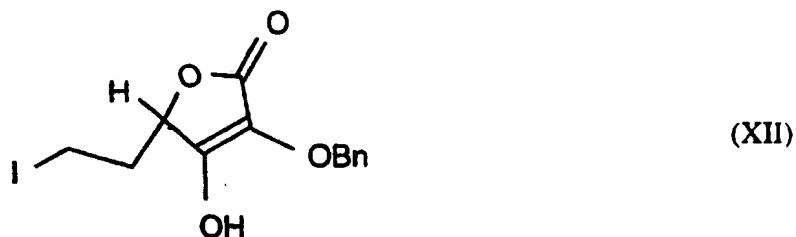
wherein Aryl and Bn are as hereinbefore defined, L is an oxygen, ester, N-sulfonamide or N-imide linkage and  $n = 2$ ; and

- 10 (c) cleaving the benzyl protecting groups of formula XI by catalytic hydrogenation to yield the desired 5-substituted-3,4-dihydroxy-2(5*H*)-furanone of the general formula I wherein R is hydrogen, Aryl is as hereinbefore defined, m is 1,  $n = 2$ , and L is an oxygen, ester, N-sulfonamide or N-imide linkage.

- 15 A process for the synthesis of analogs of the formula I wherein R is hydrogen, Aryl is as hereinbefore defined, m is 1,  $n = 2$ , and L is a sulfur linkage comprises:

(a) Iododination of the 3-benzyloxy-4-hydroxy-5-(2-hydroxyethyl)-2(5*H*)-furanone of the formula IX with  $I_2$ ,  $PPh_3$  and imidazole in  $CH_3CN$ /ether (1/5) to produce the 3-benzyloxy-4-hydroxy-5-(2-iodoethyl)-2(5*H*)-furanone of formula,

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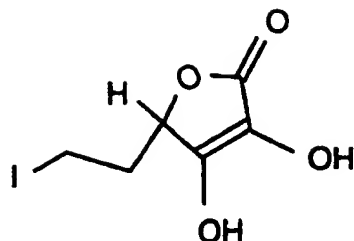


wherein Bn is as hereinbefore defined;

- 30 (b) benzyl group cleavage by first treating the furanone of formula XII with acetyl anhydride and pyridine in  $CH_2Cl_2$  for 2 hours, followed by removal of all volatile substances in vacuo and subsequent treatment with boron trichloride to yield 3,4-dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone of the formula;

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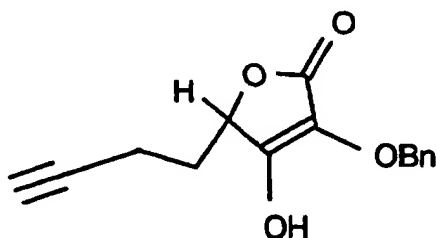
(XIII)

10 (c) reaction of a compound with the formula XIII with three mole equivalents of the lithium salt of an arylthiol, wherein aryl is as hereinbefore defined, provides compounds of the formula I wherein Aryl is as hereinbefore defined,  $n = 2$ ,  $R = H$ , and L is sulfur.

15 A process for the synthesis of analogs of the formula I wherein R is hydrogen, Aryl is as hereinbefore defined, m is 1,  $n = 2$ , and L is an acetylene or carbon-carbon double bond linkage comprises:

(a) reaction of 5-(2-iodoethyl)-2-(5H)-furanone of the formula XII with lithium acetylide ethylenediamine complex in HMPA at  $-5^{\circ}\text{C}$  to make 3-benzyloxy-4-hydroxy-5-(3-butynyl)-2-(5H)-furanone of formula,

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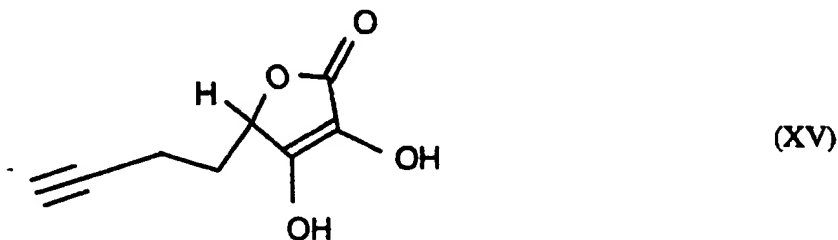
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wherein Bn is as hereinbefore defined;

(b) benzyl group cleavage by first treating the furanone of formula XIV with acetyl anhydride and pyridine in  $\text{CH}_2\text{Cl}_2$  for 2 hours, followed by removal of all volatile

substances in vacuo and subsequent treatment of the remaining residue with boron trichloride to yield compounds of the general formula;

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(c) coupling the 5-(3-butynyl)-2(5H)-furanone of formula XV with an aryl iodide to provide analogs of the formula I, wherein Aryl is as hereinbefore defined,  $n = 2$ ,  $R = H$  and L is an acetylene linker;

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(d) reduction of the acetylene moiety by the addition of 1 mole equivalent of  $H_2$  by catalytic hydrogenation under Lindlar conditions to yield compounds of formula I wherein Aryl is as hereinbefore defined,  $n = 2$ ,  $R = H$  and L is a carbon-carbon *cis* double bond; and

(e) reduction of the acetylene moiety by the addition of 2 mole equivalent of  $H_2$  by catalytic hydrogenation to yield compounds of formula I wherein Aryl is as hereinbefore defined,  $m = 0$ ,  $n = 4$ , and R is hydrogen.

20

In a composition aspect, the present invention encompasses novel pharmaceutical compositions comprising the compounds of the general formula I, together with a physiologically acceptable carrier or excipient, in an amount sufficient to have antilipidemic, antiaggregatory or antiinflammatory activities in an animal or patient. The compounds and their compositions of the present invention are thus useful in the treatment or prevention of atherosclerotic disorders, as well as in the treatment of various pathologies in which acute and chronic inflammation occur.

25

30

The starting materials utilized in the synthesis of the compounds of formula I are known in the art and/or are preparable by methods described herein. Where the pure optical isomers of these compounds are desired, numerous methods exist for the manufacture of optically active and optically pure derivatives of the necessary starting materials.

35

Also, a wide range of chiral bases can be used to starting materials and



intermediate products. Partial separation of enantiomers can typically accomplished with optically active solvents such as (-)-menthone, (-)-menthyl acetate and (+)-limonene. Anion-exchange chromatography using a chiral stationary phase constructed of 1-p-nitrophenyl-2-amino-1,3-propanediol, or chromatography through starch successfully separates mandelic acid enantiomers.

The invention also provides for pharmaceutical compositions comprising the compounds of formula I above, as well as their physiologically acceptable salts (such as, for example,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{NH}_4^+$ ).

The compounds of the invention have antilipidemic and antiaggregatory activity and are thus useful in the treatment or prevention of atherosclerotic disorders. Additionally, the compounds of the invention possess the ability to inhibit the activity of cyclooxygenase and 5-lipoxygenase in standardized assays for such activity, thus making them useful for the treatment of pathologies involving acute or chronic inflammation, such as inflammatory bowel disease, asthma, adult respiratory distress syndrome (ARDS) and various forms of arthritis.

### BIOLOGICAL EVALUATION

The compounds of the invention were screened for their anti-inflammatory activity using a series of *in vitro* tests the details of which are given below. The activity of various compounds against 5-lipoxygenase, cyclooxygenase-1, cyclooxygenase-2 and lipid peroxidase was evaluated. Results of the screening procedures are included in TABLE I, and the activity against 5-lipoxygenase at a test concentration of  $1\mu\text{M}$  in Table II.

### 5-LIPOXYGENASE SCREEN

5-Lipoxygenase catalyzes the oxidative metabolism of arachidonic acid to 5-hydroperoxyeicosatetraenoic acid (5-HETE), the initial reaction leading to the

formation of the leukotrienes. Briefly, the testing procedure utilizes a crude enzyme preparation from rat basophilic leukemia cells (RBL-1) according to the methods of T. Shimizu et al. *Pro. Natl. Acad. Sci.* 81:689-693 (1984) and R.W. Egan et al, *J. Biol. Chem.* 260: 11554-11559 (1985). Test compounds are pre-incubated with the enzyme  
5 preparation for 5 minutes at room temperature and the reaction is initiated by the addition of arachidonic acid. Following an 8 minute incubation at room temperature, the reaction is terminated by the addition of citric acid and concentrations of 5-HETE are determined by RIA. Compounds are screened at 30 $\mu$ M. Under these conditions the reference compound phenidone has an IC<sub>50</sub> of 30 $\mu$ M.

#### 10 CYCLOOXYGENASE-1 SCREEN

Cyclooxygenase-1 is involved in the formation of prostaglandins and thromboxane via the oxidative metabolism of arachidonic acid. Briefly, cyclooxygenase from ram seminal vesicles is incubated with arachidonic acid (100 $\mu$ M) for 2 minutes at 37°C in the presence or absence of test compounds according to the methods of A.T. Evans et  
15 al., *Biochem. Pharm.* 36:2035-2037 (1987) and R. Boopathy et al., *Biochem J.* 239:371-377 (1968). The assay is terminated by the addition of trichloroacetic acid and cyclooxygenase activity is determined by reading the absorbance at 530nm. Compounds are screened at 300 $\mu$ M. Under these condition the reference compound aspirin has an IC<sub>50</sub> value of 240 $\mu$ M.

#### 20 CYCLOOXYGENASE-2 SCREEN

Cyclooxygenase-2, also known as prostaglandin H synthetase-2, catalyzes the rate-limiting step in the synthesis of inflammatory prostaglandins. In this reaction cyclooxygenase-2 catalyzes the oxygenation of unesterified precursors to form cyclic endoperoxide derivatives, including prostaglandin H. Briefly, cyclooxygenase-2 from  
25 sheep placenta, 14 $\mu$ g/assay tube, is incubated with arachidonic acid (500 $\mu$ M) for 1.5 minutes at 27°C in the absence or presence of test compounds according to the methods of A.T. Evans, et al., *Biochem Pharm.* 36:2035-2037 (1987) and M.G. O'Sullivan et al., *Biochem. Biophys. Res. Cxomm.* 187: 1123-1127 (1992). The assay

is terminated by the addition of trichloroacetic acid and cyclooxygenase activity is determined by reading the absorbance at 532nm. Compounds are screened at 300 $\mu$ M. Under these conditions the reference compound NS-398 exhibited 77% inhibition at 300 $\mu$ M.

5

#### LIPID PEROXIDATION SCREEN

Lipid peroxidation is a consequence of various stimuli, including reactive free radicals. Polyunsaturated fatty acids associated with plasma membranes are degraded due to enzymatic induction by reactive agents such as CCl<sub>4</sub>, leading to cellular damage. Briefly, microsomes are prepared from rat livers and the protein concentration is determined according to the method of D. Mansuy et al., *Biochem. Biophys. Res. Comm.* 135:1015-1021 (1986). A reaction mixture consisting of 2mg of the microsomal preparation, an NADPH generating system, 20mM CCl<sub>4</sub> and test compound are incubated for 12 minutes at 37°C. The reaction is terminated by the addition of a mixture of thiobarbituric acid and trichloroacetic acid. The absorbance is read at 535nm and is proportional to the concentration of malondialdehyde. Compounds are screened at 300 $\mu$ M. Under these conditions the reference compound, alpha-tocopherol has an IC<sub>50</sub> value of 280 $\mu$ M.

TABLE I

		(PERCENT INHIBITION)				
Example #	Compound Name	COX-1 (300μM)	COX-2 (300μM)	5-LO (30μM)	LPO (300μM)	
1	3,4-Dihydroxy-5-methyl-5-phenyl-2(5H)-furanone	-12	3	58	63	
2	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5H)-furanone	33	22	107	78	
3	3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5H)-furanone	2	-4	99	78	
4	5-(4-Chlorophenyl)-3,4-dihydroxy-5-methyl-2(5H)-furanone	2	24	2	54	
5	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-propyl-2(5H)-furanone	13	22	99	70	
6	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-(2-methylpropyl)-2(5H)-furanone	67	46	96	82	
7	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5H)-furanone	52	34	102	73	
8	3,4-Dihydroxy-5,5-diphenyl-2(5H)-furanone	15	17	94	70	
9	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-(1-propyl)-2(5H)-furanone	25	19	82	79	
10	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-phenyl-2(5H)-furanone	43	34	106	89	
11	(S)-(+)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5H)-furanone	34	10	101	71	
12	(R)-(-)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5H)-furanone	10	12	101	62	
13	(R)-(-)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5H)-furanone	12	14	102	76	
14	(S)-(+)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5H)-furanone	12	18	96	66	
15	3,4-Dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5H)-furanone	9	-4	100	-5	
16	3,4-Dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5H)-furanone	17	2	100	76	
17	5-[2-(Dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5H)-furanone	17	21	99	74	
18	3,4-Dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5H)-furanone	11	-12	99	71	
19	3,4-Dihydroxy-5-[2-(1,8-naphthalimide)-N-ethyl]-2(5H)-furanone	9	2	86	68	

20	3,4-Dihydroxy-5-[2-(1,8-naphthosuliam)-N-ethyl]-2(5H)-furanone	-15	13	91	61
21	3,4-Dihydroxy-5-[2-(diphenylmethane-2-oxylethyl)-2(5H)-furanone	12	10	101	68
22	5-[2-((1,1'-Biphenyl)-4-oxylethyl)-3,4-dihydroxy-2(5H)-furanone	18	10	99	74
23	3,4-Dihydroxy-5-[2-(quinoline-2-oxylethyl)-2(5H)-furanone	8	-2	93	69
24	3,4-Dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5H)-furanone	76	68	113	78
25	3,4-Dihydroxy-5-[2-(naphthyl-1-thio)ethyl]-2(5H)-furanone	6	19	102	74
26	3,4-Dihydroxy-5-[2-(naphthyl-2-thio)ethyl]-2(5H)-furanone	12	12	101	77
27	3,4-Dihydroxy-5-[(4-phenyl)-3-butyryl]-2(5H)-furanone	5	20	42	59
28	3,4-Dihydroxy-5-[(4-(2-methyl)phenyl)-3-butyryl]-2(5H)-furanone	4	15	58	61
29	3,4-Dihydroxy-5-[(4-(2-hexenyl))phenyl]-3-butyryl]-2(5H)-furanone	55	26	81	72
30	3,4-Dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butyryl]-2(5H)-furanone	26	16	100	62
31	3,4-Dihydroxy-5-[(4-(2-phenylsulfonamide-(N-butyryl)-3-butyryl)-2(5H)-furanone	7	23	81	73
32	3,4-Dihydroxy-5-[4-(2-naphthyl)-3-butyryl]-2(5H)-furanone	34	23	98	75
33	3,4-Dihydroxy-5-[(4-(2-(propylthio)methyl)phenyl)-3-butyryl]-2(5H)-furanone	37	: 20	84	74
34	3,4-Dihydroxy-5-[(4-(2-(1-pentylthio)methyl)phenyl)-3-butyryl]-2(5H)-furanone	67	43	92	63
35	3,4-Dihydroxy-5-[(4-(2-(propylsulfonyl)methyl)phenyl)-3-butyryl]-2(5H)-furanone	25	13	30	60
36	3,4-Dihydroxy-5-[2-(4-(4-fluorophenyl)methyl)thiophene)-(3-butyryl)]-2(5H)-furanone	NT	NT	85@1	NT
37	furanone				
38	3,4-Dihydroxy-5-(4-phenylbutanyl)-2(5H)-furanone	NT	NT	NT	NT
39	3,4-Dihydroxy-5-[(4-phenyl)-3Z-butenyl]-2(5H)-furanone	NT	NT	NT	NT
40	3,4-Dihydroxy-5-[(4-(2-methyl)phenyl)-3Z-butenyl]-2(5H)-furanone	NT	NT	NT	NT
	3,4-Dihydroxy-5-[(4-(2-(2Z-hexenyl))phenyl)-3Z-butenyl]-2(5H)-furanone	38	25	99	65

**TABLE II**  
**The effect of various aci-reductones on 5-Lipoxygenase (5-LO)**  
 at a test concentration of 1µM

Example #	Compound Name	Percent Inhibition of 5-LO at a test Conc. of (1µM)
5		15
2	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5H)-furanone	68
5	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-propyl-2(5H)-furanone	70
6	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-(2-methylpropyl)-2(5H)-furanone	61
7	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5H)-furanone	15
10	3,4-Dihydroxy-5,5-diphenyl-2(5H)-furanone	40
9	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-(1-propyl)-2(5H)-furanone	64
10	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-phenyl-2(5H)-furanone	59
11	(S)-(+)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5H)-furanone	60
12	(R)-(-)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5H)-furanone	59
13	(R)-(-)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5H)-furanone	50
14	(S)-(+)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5H)-furanone	52
15	3,4-Dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5H)-furanone	54
16	3,4-Dihydroxy-5-[2-(flavone-6-oxyethyl)-2(5H)-furanone	60
17	5-[2-(Dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5H)-furanone	49
18	3,4-Dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5H)-furanone	38
20	3,4-Dihydroxy-5-[2-(1,8-naphthosultam)-N-ethyl]-2(5H)-furanone	62
21	3,4-Dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5H)-furanone	55
22	5-[2-((1,1'-Biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5H)-furanone	71
24	3,4-Dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5H)-furanone	56
25	3,4-Dihydroxy-5-[2-(naphthyl-1-thio)ethyl]-2(5H)-furanone	

26	3,4-Dihydroxy-5-[2-(naphthyl-2-thio)ethyl]-2(5H)-furanone	54
29	3,4-Dihydroxy-5-[(4-(2-(2Z-hexenyl))phenyl)-3-butyryl]-2(5H)-furanone	56
30	3,4-Dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butyryl]-2(5H)-furanone	70
32	3,4-Dihydroxy-5-[4-(2-naphthyl)-3-butyryl]-2(5H)-furanone	66
46	3,4-Dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butyryl)]-2(5H)-furanone	91; IC <sub>50</sub> = 160nM
5		

Nuclear factor- $\kappa$ B exists in the cytoplasm of most cells bound to a natural inhibitor protein I $\kappa$ B. In a complex cascade, extracellular stimulation by cytokines such as TNF- $\alpha$  or interleukin-1 (IL1), viruses, lipopolysaccharide (LPS) or UV-radiation results in the production of second messenger reactive oxygen species (ROS).

- 5 Increased ROS concentrations are important mediators, which instigate the process of I $\kappa$ B disassociation from the NF- $\kappa$ B complex enabling NF- $\kappa$ B to migrate into the cell nucleus. Recent findings demonstrate that low levels of H<sub>2</sub>O<sub>2</sub> activate NF- $\kappa$ B and that a number of antioxidants inhibit this activation process. The antioxidants pyrrolidone dithiocarbamate (PDTC) and N-acetyl-cysteine (NAC) inhibit both the
- 10 H<sub>2</sub>O<sub>2</sub> and extracellular cytokine-induced activation of NF- $\kappa$ B in a concentration dependent manner. Steroids such as dexamethasone are potent anti-inflammatory agents in part, because they stimulate the gene synthesis of I $\kappa$ B, leading to inhibition of NF- $\kappa$ B. The mechanism by which these aci-reductones block NF- $\kappa$ B nuclear translocation is not clear, but is likely related to their antioxidant properties.
- 15 However, the possibility that they specifically interact with a biomolecule involved in NF- $\kappa$ B activation has not been disregarded.

Test Compound	Concentration	% Inhibition
3,4-Dihydroxy-5-[4-(2-naphthyl)-3-butyryl]-2(5H)-furanone	30nM	90%
Reference Compounds		
Dexamethasone	1000nM	60%
Pyrrolidone dithiocarbamate (PDTC)	10,000nM	50%
N-Acetyl-cysteine (NAC)	1000nM	0%

- Experiments measuring test agents effect on NF- $\kappa$ B nuclear membrane translocation
- 25 were performed with NR8383 cells, which are transformed rat alveolar macrophages. Cells were treated simultaneously with LPS (1  $\mu$ g/ml) and the test compounds (10 and 30 nM). In addition, some compounds were tested at doses of 10 and 30  $\mu$ M. Untreated control cells and cells treated with LPS alone were tested in each experiment. Cells were harvested 6 hours after treatment. Nuclear proteins
- 30 were extracted, frozen and quantified using the Bradford assay. Electrophoretic



mobility shift assays (EMSA) were subsequently analyzed using a radiolabeled NF- $\kappa$ B probe. Nuclear proteins were reacted with the radiolabeled probe, run on a 5% polyacrylamide gel, and subjected to autoradiography. Specificity of protein binding for the NF- $\kappa$ B binding site was assayed by cold and nonspecific competition using the LPS treated sample in each experiment. All EMSA were duplicated at least once to verify results. Laser densitometry of NF- $\kappa$ B bands was done on autoradiographs to quantify NF- $\kappa$ B binding activity.

The human T lymphoid cell line Jurkat was transfected with a response element lacZ reporter in which transcription of the  $\beta$ -galactosidase gene is directed by the binding site for the NF- $\kappa$ B transcription factor. The cell line containing  $\kappa$ B-Z is stimulated with calcium ionophore A23187 and phorbol ester PMA; this stimulation is inhibited by the immunosuppressive drug cyclosporin A. In the screening assay transfected  $\kappa$ B-Z Jurkat cells ( $1 \times 10^6$  cells/assay well) are incubated with 2 $\mu$ M A23187, 20 ng/mL PMA and test compound or vehicle in the well of a microplate for at least 4 hours according to the procedure of M.J. Lenardo and D. Baltimore, NF- $\kappa$ B: a pleiotropic mediator of inducible and tissue specific gene control. *Cell* 58, 227-229, (1989). At the end of the incubation, the cells are spun down and resuspended in the buffer and FDG (fluorescein di- $\beta$ -D-galactopyranoside) solution. The covered plates are further incubated in the dark for 16 hours at 25°C. The fluorescent product resulting from the end of reaction is read at 485/530 in a Cyto2300 fluorescence reader. Compounds were screened at 10 $\mu$ M. The standard, cyclosporin A has an IC<sub>50</sub> of 50nM in this assay.

TABLE III

The effect of various aci-reductones on Nuclear Factor-kappa B

		Percent Inhibition (%)		(PERCENT INHIBITION)	
5	Example #	Compound Name	NF-κB (10 μM)		
10	2	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5H)-furanone	90		
	5	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-propyl-2(5H)-furanone	68		
	6	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-(2-methylpropyl)-2(5H)-furanone	59		
	7	5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5H)-furanone	21		
	8	3,4-Dihydroxy-5,5-diphenyl-2(5H)-furanone	33		
15	9	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-(1-propyl)-2(5H)-furanone	26		
	10	3,4-Dihydroxy-5-(4-isobutylphenyl)-5-phenyl-2(5H)-furanone	16		
	11	(S)-(+)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5H)-furanone	72		
	12	(R)-(-)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5H)-furanone	56		
	13	(R)-(-)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5H)-furanone	49		
41	14	(S)-(+)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5H)-furanone	60		
	24	3,4-Dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5H)-furanone	44		
	41	3,4-Dihydroxy-5-[2-(4-(4-fluorophenyl)methyl)thiophene)-(3-butynyl)]-2(5H)-furanone	61; IC <sub>50</sub> = 6 μM		

The ability of the compounds of formula I to inhibit the action of various inflammatory cytokines make them useful in a wide variety of therapeutic methods. Specifically, their ability to mediate or inhibit the actions of TNF- $\alpha$  makes these compounds useful in the treatment of various invasive diseases, infections, and inflammatory states. Particularly important is the inhibition of the large amount of TNF produced during serious bacterial infections, which can trigger a state of shock and tissue injury (septic shock syndrome).

A further important use of the compounds of formula I is to inhibit the TNF which is known to mediate cachexia produced during chronic disease states. Thus, these compounds are particularly useful in adjunctive therapy for AIDS and cancer patients to reduce and/or ameliorate the consequences of cachexia produced during these chronic disease states.

A further specific method of treatment for which the compounds of the instant invention are particularly useful is in the treatment of rheumatoid arthritis wherein increased amounts of the inflammatory cytokines, TNF- $\alpha$  and IL-1 are present. By virtue of their ability to mediate and/or inhibit the action of these cytokines, inflammation and the severity of the disease state can be reduced or eliminated.

The compounds of the instant invention can also be utilized in the treatment of multiple sclerosis (MS), Crohn's disease and ulcerative colitis by inhibiting and the activity of the inflammatory cytokines which underlie these disease states.

The compounds of the invention may be formulated in a conventional manner, optionally together with one or more other active ingredients, for administration by any convenient route for example of oral, intravenous or intramuscular administration.

Thus, according to another aspect, the invention provides a pharmaceutical composition comprising a compound of formula I and/or a pharmaceutically

acceptable salt thereof together with a pharmaceutically acceptable carrier or excipient.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by  
5 conventional means with physiologically acceptable excipients.

The compounds may be formulated for intravenous or intramuscular administration in dry form for reconstitution before use, or as a sterile solution or suspension.

A proposed daily dose based on similar pharmacokinetic parameters to CHTA for administration to man is about 10 to 25 mg/kg, for example, 700 mg to 1 gm daily,  
10 which may be conveniently administered in 1 to 3 doses per day. The precise dose administered will, of course, depend on the age and condition of the patient.

The following examples are illustrative of the present invention.

### EXAMPLES

**General Methods.** Unless otherwise noted all reagents were purchased from  
15 commercial suppliers and used as received. Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt Apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained with either an IBM-Bruker model NR/100 or Varian model 200 FT NMR spectrometer. Tetramethylsilane (TMS) in CDCl<sub>3</sub>, DMSO-*d*<sub>6</sub>, acetone-*d*<sub>6</sub>, CD<sub>3</sub>OD or D<sub>2</sub>O was used as internal standard. Chemical shifts  
20 are reported on the  $\delta$  scale with peak multiplicities: s, singlet; d, doublet; dd, doublet of doublets; ddd doublet of doublet of doublets; t, triplet; q, quartet, m, multiplet. Anhydrous solvents were purchased from Aldrich Chemical, Inc., Milwaukee, WI and used as such. Optical rotations were performed on a Perkin-Elmer model 241

polarimeter using a 10 cm, 1mL cell. Elemental Analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ.

### PREPARATION OF STARTING MATERIALS

#### EXAMPLE A

##### 5                    **Ethyl 4-phenylbenzoylformate**

A mixture of 77g (500mmol) of biphenyl and 68mL (540mmol) of ethyl oxalylchloride was dissolved in 300mL of 1,2-dichloroethane and cooled with stirring to between 0° and 10°C. AlCl<sub>3</sub> (73g, 550mmol) was added at such a rate to maintain the reaction temperature below 15°C. The mixture was stirred at 10°C for 1 hour and  
10 at 25°C for 24 hours, then poured into 1000mL of a ice cold 10% HCl solution. The aqueous suspension was extracted with 4 x 500mL of ether and the combined ether extracts were washed with 100mL of 10% HCl solution, 100mL of brine, dried (MgSO<sub>4</sub>) and concentrated to a yellow oil which was purified by chromatography over SiO<sub>2</sub> using initially acetone/hexanes (2/98) and increasing the polarity of the solvent  
15 to acetone/hexanes (10/90) upon elution of the nonpolar impurities to liberate 82g (68% yield) of a yellow oil, which crystallized on standing.

#### EXAMPLE B

##### **Ethyl 4-isobutylbenzoylformate**

A mixture of 27g (200mmol) of isobutylbenzene and 24mL (215mmol) of ethyl  
20 oxalylchloride underwent Friedel-Crafts acylation reaction in an analogous fashion as described for the synthesis of ethyl 4-phenylbenzoylformate to yield 38g (81% yield) of ethyl 4-isobutylbenzoylformate as a colorless oil.

#### EXAMPLE C

##### **3-Benzyloxy-4-hydroxy-5-(2-hydroxy)ethyl-2(5H)-furanone**

25 A. A solution of 10.0g (98mmol) of  $\alpha$ -hydroxy- $\gamma$ -butyrolactone in 100mL of anhydrous THF under argon was cooled to 0-5°C with magnetic stirring. Addition of 14mL (110mmol) of trimethylsilyl chloride and 16mL (115mmol) of triethylamine

immediately produced a white precipitate. The suspension was warmed to room temperature and stirred for 4 hours. The suspension was poured into a separatory funnel containing 100mL of H<sub>2</sub>O and 500mL of ether. The organic layer was washed with 50mL of H<sub>2</sub>O, 50mL of brine, dried (MgSO<sub>4</sub>) and concentrated. Purification  
5 (Kugelrohr distillation) provided 14.7g (90% yield) of  $\alpha$ -trimethylsilyloxy- $\gamma$ -butyrolactone bp 80-100°C (8 mm Hg).

B. To a 500mL 2-necked flask flame dried under argon and equipped with a magnetic stir bar, was added 200mL of THF and 18.7mL (89mmol) of hexamethyldisilazide. The flask was cooled to -78°C and 55.4mL (89mmol) of a 1.6M nBuLi solution in  
10 hexanes was added with stirring over 15 min. The light yellow solution was stirred for an additional 15 min and 16.7g (86mmol) of ethyl benzyloxyacetate was added over 5 min. The solution was stirred for 20 min at -78°C, and 14.7g (84.4mmol) of  $\alpha$ -silyloxy- $\gamma$ -butyrolactone was added via syringe. The reaction mixture was quenched after 30 minutes by pouring into a mixture of 100mL of 10% aqueous HCl solution  
15 and 500mL of ether. The aqueous layer was separated and washed with 2 x 100mL of ether. The combined ether extracts were washed with 50mL of brine, dried (MgSO<sub>4</sub>) and concentrated leaving a yellow oil, which was dried *in vacuo* for 15 hours.

C. The yellow oil was placed under argon, diluted with 400mL of MeOH, cooled to 0°C with stirring and 11.7g (85mmol) of anhydrous K<sub>2</sub>CO<sub>3</sub> was added. After 30  
20 minutes the suspension was concentrated to a volume of about 75mL, diluted with 100mL of H<sub>2</sub>O and 50mL of saturated sodium bicarbonate solution, and washed with 2 x 100 mL of ether. The aqueous phase was acidified with 37% HCl solution to a pH near 1 and extracted with 10 x 150mL of ether. The combined ether extracts were washed with 100mL of brine, dried (MgSO<sub>4</sub>) and concentrated to a yellow oil (18.7 g,  
25 86%) which solidified upon standing. Recrystallization from benzene and hexanes provided 15.8 g, (75% yield) of 3-benzyloxy-4-hydroxy-5-(2-hydroxy)ethyl-2(5H)-furanone as a white solid: mp 98-99°C, <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>)  $\delta$  7.46-7.27 (m, 5H),

5.06 (s, 2H), 4.83 (t,  $J = 6.3$  Hz, 1H), 3.85-3.69 (m, 2H), 2.05-1.95 (m, 1H), 1.89-1.76 (m, 1H). Anal Calcd for  $C_{13}H_{14}O_5$ : C, 62.39; H, 5.64. Found: C, 62.51; H, 5.50.

#### EXAMPLE D

##### 3,4-Dibenzyloxy-5-(2-hydroxyethyl)-2(5H)-furanone

- 5 A mixture of 1.25g (5mmol) of 3-benzyloxy-4-hydroxy-5-(2-hydroxyethyl)-2(5H)-furanone, 15mL of THF, 871 $\mu$ L (5.0mmol) of diisopropylethylamine and 631 $\mu$ L (5.2mmol) of benzyl bromide were combined under argon. The reaction mixture was warmed to reflux for 5 hours, and upon cooling, a suspension formed which was poured into 50mL of 5% aqueous HCl solution and extracted with 100mL of ether.
- 10 The ether fraction was separated and sequentially washed with 30mL of 5% aqueous HCl, 30mL of  $H_2O$ , 30mL of saturated  $NaHCO_3$  solution, 30mL of  $H_2O$ , 30mL of brine, dried ( $MgSO_4$ ) and concentrated to a colorless oil. Purification over silica gel using EtOAc/hexanes (2/3) provided 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5H)-furanone as a faint pink colored oil (1.0g, 60% yield).

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#### EXAMPLE E

##### 3-Benzyloxy-4-hydroxy-5-(2-iodoethyl)-2(5H)-furanone

- To an oven dried 250mL round bottom flask flushed with argon was added 5.8g (22mmol) of  $PPh_3$ , 1.5g (22mmol) of imidazole and 80mL of ether/ $CH_3CN$  (3/1). The mixture was cooled in an ice water bath with magnetic stirring and 5.6g (22mmol) of
- 20 iodine was added in 4 equal portions with vigorous stirring. The resulting slurry was warmed at room temperature for 20 minutes, cooled to  $0^\circ C$ , and 5.0g (20mmol) of 3-benzyloxy-4-hydroxy-5-(2-hydroxyethyl)-2(5H)-furanone dissolved in 20mL of  $CH_3CN$ /ether (1/1) was added in one portion and the remainder was rinsed in with 5mL of ether. The mixture was stirred at  $0^\circ C$  for 10 minutes, then at room
- 25 temperature for 30 minutes and quenched by pouring into 150mL of 10% HCl solution and extracting with 500mL of ether/hexanes (1/1). The aqueous layer was separated and extracted with 100mL of ether. The combined organic fractions were washed with 50mL of  $H_2O$  and extracted with 5 x 50mL of saturated  $NaHCO_3$

solution. The combined bicarbonate extracts were washed with 50mL of ether/hexanes (1/1), acidified to pH below 2 with 10% HCl solution and extracted with 3 x 200mL of ether. The combined ether extracts were washed with 100mL of brine, dried (MgSO<sub>4</sub>) and concentrated to give 6.7g, (93% yield) of 3-benzyloxy-4-hydroxy-5-(2-iodoethyl)-2(5*H*)-furanone as a white solid, which was not further purified: mp 101-104°C, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.40-7.27 (m, 5H), 5.06, (dd, J = 11.4 Hz, 2H), 4.69 (dd, J = 3.4, 8.0 Hz, 1H), 3.06 (t, J = 7.3 Hz, 2H), 2.41-2.29 (m, 1H), 2.02-1.90 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 170.33, 160.61, 136.32, 128.77, 128.69, 128.58, 120.11, 75.76, 73.39, 35.77, -2.03; Anal Calcd for C<sub>13</sub>H<sub>13</sub>O<sub>4</sub>I: C, 43.35; H, 3.64. Found: C, 43.94; H, 3.69.

### EXAMPLE F

#### 3,4-Dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone

To a dry flask flushed with argon was added 0.72g (2.0mmol) of 3-benzyloxy-4-hydroxy-5-(2-iodoethyl)-2(5*H*)-furanone and 10mL of CH<sub>2</sub>Cl<sub>2</sub>. The solution was cooled with stirring in an ice-water bath, and 0.38mL (4.0mmol) of acetic anhydride and 0.34mL (4.2mmol) of pyridine were added. The ice bath was removed and the solution was stirred for 1 hour. All volatile substances were removed *in vacuo* (2h at 1 mm Hg, 25°C). Argon was introduced to the reaction flask and the residue was taken up in 20mL of dry CH<sub>2</sub>Cl<sub>2</sub>, cooled to -78°C and 5.2mL (2.6mmol) of 1.0M BCl<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> was added with stirring. The reaction mixture was kept at -78°C for 1 hour and at room temperature for 30 minutes. The mixture was poured into 50mL of brine and extracted with 3 x 30mL of ether. The combined ether extracts were washed with 5mL of H<sub>2</sub>O and extracted into saturated NaHCO<sub>3</sub> solution (3 x 15mL). The bicarbonate fractions were pooled and washed with 15mL of ether, acidified to pH 1 with 25% aqueous HCl solution, and extracted with 3 x 30mL of ether. The ether extracts were combined and washed with 15mL of brine, dried (MgSO<sub>4</sub>) and concentrated to provide 360mg (67% yield) of 3,4-dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone as a white crystalline solid: mp 150-151°C; <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 4.80



(dd, 1H,  $J = 3.5, 8.0$  Hz), 3.50-3.25 (m, 2H), 2.60-2.35 (m, 1H), 2.20-1.95 (m, 1H).

Anal Calcd for  $C_8H_7O_4I$ : C, 26.69; H, 2.61. Found: C, 26.54; H, 2.59.

### EXAMPLE G

#### 5                    3-Benzoyloxy-5-(3-butyne)-4-hydroxy-2(5H)-furanone

To a flame-dried three-necked round bottom flask with magnetic stir bar, argon inlet, and septum containing 5.7g (55.8mmol) of 90% lithium acetylide ethylenediamine complex, was added 20mL of HMPA. The suspension was stirred for 15 minutes at room temperature, cooled in an ice bath (acetone/ $CO_2$ ) to between  $-5^\circ C$  and  $-10^\circ C$ ,  
10 and 6.7g (18.6 mmol) of 3-benzoyloxy-4-hydroxy-5-(2-iodoethyl)-2(5H)-furanone dissolved in 15mL of HMPA was added over a two minute period. A dark brown-orange slurry formed and the temperature was maintained between  $0^\circ C$  and  $-5^\circ C$  for 30 minutes. The mixture was quenched by the careful addition of 150mL of 10% aqueous HCl solution, which was immediately extracted with 2 x 200mL of ether.  
15 The combined ether extracts were washed with 2 x 50mL of 5% aqueous HCl solution and extracted with 4 x 50mL of  $NaHCO_3$  solution. The combined bicarbonate extracts were washed with 50mL of ether, acidified with 20% aqueous HCl solution to pH 1 and extracted with 3 x 150mL of ether. The combined ether extracts were washed with 50mL of brine, dried ( $MgSO_4$ ) and concentrated leaving 4.1 g (85%  
20 crude yield) of 3-benzoyloxy-5-(3-butyne)-4-hydroxy-2(5H)-furanone as a yellow solid. This material was used without further purification in subsequent steps: mp  $85-88^\circ C$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.38-7.26 (m, 5H), 5.06, (q,  $J_{ab} = 11.6$  Hz, 2H), 4.75 (dd,  $J = 3.5, 8.1$  Hz, 1H), 2.27-2.20 (m, 2H), 2.12-2.01 (m, 1H), 1.98 (t,  $J = 2.6$  Hz, 1H), 1.73-1.62 (m, 1H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  169.93, 160.90, 136.39, 128.77, 128.73,  
25 128.64, 120.13, 82.31, 74.30, 73.43, 69.71, 30.78, 13.72.

### EXAMPLE H

#### 5-(3-Butyne)-3,4-dihydroxy-2(5H)-furanone

An oven dried 250mL flask equipped with a magnetic stir bar was flushed with argon and charged with 2.6g (10.0mmol) of 3-benzoyloxy-5-(3-butyne)-4-hydroxy-2(5H)-

furanone and 50mL of anhydrous  $\text{CH}_2\text{Cl}_2$ . The solution was cooled in an ice bath to 5°C with magnetic stirring and 1.9mL (20.0mmol) of acetic anhydride was added followed by 1.7mL (21mmol) of pyridine. The ice bath was removed after 1 hour, and the mixture was concentrated on a rotary evaporator and dried at 0.5 mm Hg at 25°C for 12 hours. Argon was introduced followed by 100mL of dry  $\text{CH}_2\text{Cl}_2$ . The solution was cooled to -78°C with stirring and 25mL (25mmol) of 1.0M  $\text{BCl}_3$  in  $\text{CH}_2\text{Cl}_2$  was added. The reaction mixture was allowed to gradually warm to 10°C over a 2 hour period and maintained at 10°C for 1 hour. The mixture was poured into 50mL of brine and extracted with 4 x 100mL of ether. The combined ether fractions were extracted with 3 x 25mL of saturated  $\text{NaHCO}_3$  solution. The combined bicarbonate extracts were washed with 25mL of ether and acidified to pH 1 with aqueous HCl solution and extracted with 5 x 100mL of ether. The combined ether washes were dried ( $\text{MgSO}_4$ ) and filtered through 100g of silica gel to remove a polar impurity using 1L of ether as eluant. Removal of solvent *in vacuo* left 1.4g (80% yield) of 5-(3-butyne)-3,4-dihydroxy-2(5H)-furanone as an off white solid: mp 124-128 °C dec.;  $^1\text{H}$  NMR (acetone-  $d_6$ )  $\delta$  4.79 (dd,  $J = 3.4, 8.3$  Hz, 1H) 2.42 (t,  $J = 2.6$  Hz, 1 H) 2.37-2.30 (m, 2H), 2.20-2.09 (m, 1H), 1.81-1.67 (m, 1H);  $^{13}\text{C}$  NMR (acetone-  $d_6$ )  $\delta$  170, 153.7, 119, 83.4, 74.7, 70.9, 32.4, 14.4; Anal Calcd for  $\text{C}_8\text{H}_8\text{O}_4$ : C, 57.14; H, 4.79. Found: C, 57.04; H, 5.01.

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### EXAMPLE I

#### 2-(2Z-Hexenyl)iodobenzene

A dry 25mL 2-necked flask equipped with a magnetic stir bar, argon inlet and septum was cooled to 0°C and 3 mL of 1.0M  $\text{BH}_3$  in THF was added. Cyclohexene, 607 $\mu\text{L}$  (6 mmol) was added via syringe and the suspension stirred at 0-5°C for 35 minutes. 2-Hexynyl iodobenzene, (0.852g, 3.0 mmol) was added to the reaction mixture dropwise over a 5 minute period, the ice bath was removed and the yellow reaction mixture stirred at room temperature for 1 hour. The solution was subsequently cooled in an ice bath, and 1.4 mL (25 mmol) of glacial AcOH was added. The mixture stirred at room temperature for 1 hour, was poured into 75mL of  $\text{H}_2\text{O}$ , and extracted

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with 3 x 30mL of hexanes. The combined hexanes fractions were washed with 25mL of H<sub>2</sub>O, 25mL of saturated NaHCO<sub>3</sub> solution, 25mL of H<sub>2</sub>O, 2 x 20mL of brine, dried (MgSO<sub>4</sub>) and concentrated to an oil (do not warm above 30°C to avoid isomerization of the double bond). Purification over 40g of silica gel using hexanes as eluant  
5 provided 670 mg (78%) of 2-(2Z-hexenyl)iodobenzene as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.82 (d, J = 7.8 Hz, 1H), 7.30-7.20 (m, 2H), 6.91-6.86 (m, 1H), 5.62-5.46 (m, 2H), 3.47 (d, J = 6.5 Hz, 2H), 2.17-2.10 (m, 2H), 1.49-1.37 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 143.8, 139.3, 131.8, 129.2, 128.3, 127.7, 126.6, 100.8, 38.8, 29.6, 22.7, 13.9; Anal Calcd for C<sub>12</sub>H<sub>15</sub>I: C, 50.37; H, 5.28. Found: C,  
10 49.97; H, 5.24.

## SYNTHESIS OF COMPOUNDS OF THE INVENTION

### EXAMPLE 1

#### **3,4-Dihydroxy-5-methyl-5-phenyl-2(5H)-furanone**

15 A. To a 2-necked flask flame dried under argon with septum and charged with a solution of 3.6g (20mmol) of ethyl benzoylformate in 50mL of anhydrous THF at -30°C was slowly added 7 mL (21mmol) of a 3.0 M solution of methylmagnesium iodide. The reaction mixture was stirred at 0°C for 45 minutes, then at room temperature for 30 minutes and again cooled to 0°C. Benzyloxyacetyl chloride  
20 (3.4mL, 21mmol) was added and the reaction mixture was stirred at room temperature for 1 hour, cooled to -78°C and 33mL of a 1.5M solution of LDA in THF was added with rapid stirring. The mixture was worked up after 1 hour by the addition of 100 mL of aqueous 10% HCl solution and 300mL of ether. The layers were separated and the organic phase was washed with 50mL aqueous 10% HCl solution, 30mL of H<sub>2</sub>O,  
25 and extracted with 3 x 40mL of saturated NaHCO<sub>3</sub> solution. The bicarbonate extracts were combined and washed with 40mL of ether, acidified to pH 1 with 10% aqueous HCl solution, and extracted with 2 x 80mL of ether. The organic fractions were combined, washed with 25 mL of H<sub>2</sub>O, 25 mL of brine, dried (MgSO<sub>4</sub>), and

concentrated leaving 1.2g (20% yield) of 4-hydroxy-5-methyl-5-phenyl-3-phenylmethoxy-2-(5*H*)-furanone as a yellow oil.

- B. The 4-hydroxy-5-methyl-5-phenyl-3-phenylmethoxy-2-(5*H*)-furanone (1.2g) was subjected to hydrogenation over 100 mg of 5% Pd/BaSO<sub>4</sub> in 100 mL of MeOH at room temperature and under 30 psi H<sub>2</sub>. The reaction was monitored periodically by TLC analysis. The suspension was filtered through two #1 filter papers, concentrated to a white solid and recrystallized from MeOH/H<sub>2</sub>O to give 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone as a white crystalline material: mp 173-175°C dec. <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.53-7.36 (m, 5H), 1.84 (s, 3H). Anal Calcd for C<sub>11</sub>H<sub>10</sub>O<sub>4</sub> + 0.125 H<sub>2</sub>O: C, 63.38; H, 4.96. Found: C, 63.30; H, 4.96.

## EXAMPLE 2

### 5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone

- A. A total of 3.4mL (10.2mmol) of 3.0M methylmagnesium iodide in THF was added to a THF solution of 2.4g (10mmol) of ethyl 4-phenylbenzoylformate in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to give prior to hydrogenolysis, 1.1g (30% yield) of 5-[(1,1'-biphenyl)-4-yl]-3-phenylmethoxy-4-hydroxy-5-methyl-2(5*H*)-furanone as a white granular solid: m.p. 182-183°C (benzene/hexanes) <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.56-7.26 (m, 14H), 5.10 (ab quartet, 2H, J = 11.4 Hz), 1.79 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 168.5, 163.8, 141.5, 140.3, 137.0, 136.3, 129.0, 128.8, 128.8, 128.8, 127.6, 127.2, 127.1, 125.6, 119.0, 81.1, 73.5, 24.3. Anal Calcd for C<sub>24</sub>H<sub>20</sub>O<sub>4</sub>: C, 77.40; H, 5.41. Found: C, 77.99; H, 5.61.
- B. Hydrogenolysis of 500 mg of the 5-[(1,1'-biphenyl)-4-yl]-3-phenylmethoxy-4-hydroxy-5-methyl-2(5*H*)-furanone was performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provided 240mg (63% yield) of 5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone as a white powder: mp 206-212°C dec. (MeOH/H<sub>2</sub>O), <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.69-7.33 (m, 9H), 1.88 (s, 3H). <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 169.5, 157.1, 141.6, 141.0, 139.8,

129.6, 128.3, 127.6, 127.6, 126.6, 117.9, 81.2, 24.5. Anal Calcd for  $C_{17}H_{14}O_4$ : C, 72.33; H, 5.00. Found: C, 72.07; H, 5.14.

### EXAMPLE 3

#### 5        **3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5H)-furanone**

A. A total of 3.4mL (10.2mmol) of 3.0M methylmagnesium iodide in THF was added to a THF solution of 2.34 g (10 mmol) of ethyl 4-isobutylbenzoylformate in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5H)-furanone to give prior to hydrogenolysis 4-hydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-3-phenylmethoxy-2(5H)-furanone in 45% yield as a yellow oil.  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.37-7.02 (m, 9H), 5.01 (s, 2H), 2.42 (d, 2H,  $J = 7.2$  Hz), 1.86-1.77 (m, 1H), 1.72 (s, 3H), 0.87 (d, 6H,  $J = 6.6$  Hz).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  170.0, 165.1, 142.1, 136.3, 135.2, 129.2, 128.9, 128.6, 127.2, 125.0, 118.6, 81.7, 73.5, 45.0, 30.2, 24.1, 22.4. Anal Calcd for  $C_{22}H_{24}O_4 + 0.5 H_2O$ : C, 73.11; H, 6.97. Found: C, 72.92; H, 6.87.

B. Hydrogenolysis of 800mg (2.3mmol) of 4-hydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-3-phenylmethoxy-2(5H)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5H)-furanone to provided 500mg (84% yield) of 3,4-dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5H)-furanone as a light yellow crystalline material: mp 135-150°C dec.  $^1H$  NMR (acetone- $d_6$ )  $\delta$  7.40-7.17 (m, 4H), 2.46 (d, 2H,  $J = 7.1$  Hz), 1.87-1.82 (m, 1H), 1.82 (s, 3H), 0.87 (d, 6H,  $J = 6.6$  Hz).  $^{13}C$  NMR (acetone- $d_6$ )  $\delta$  169.5, 157.2, 142.4, 138.0, 129.8, 125.9, 117.9, 81.3, 45.3, 30.8, 24.5, 22.5. Anal Calcd for  $C_{15}H_{18}O_4 + 0.25 H_2O$ : C, 67.53; H, 6.99. Found: C, 67.78; H, 7.09.

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### EXAMPLE 4

#### **5-(4-Chlorophenyl)-3,4-dihydroxy-5-methyl-2(5H)-furanone**

A. A total of 3.4mL (10.2mmol) of 3.0M methylmagnesium iodide was added to a solution of 2.34g (10mmol) of ethyl 4-chlorobenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5H)-

furanone to give prior to hydrogenolysis 1.3g (40% yield) of 5-(4-chlorophenyl)-4-hydroxy-5-methyl-3-phenylmethoxy-2(5*H*)-furanone as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.37-7.21 (m, 9H), 5.10 (s, 2H), 1.73 (s, 3H).

- B. Hydrogenolysis of 330 mg of 5-(4-chlorophenyl)-4-hydroxy-5-methyl-3-phenylmethoxy-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provided 110mg (46% yield) of 5-(4-chlorophenyl)-3,4-dihydroxy-5-methyl-2(5*H*)-furanone a light tan solid: mp 154-155°C dec.(benzene/hexanes) <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.52-7.34 (m, 4H), 1.82 (s, 3H). <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 169.0, 156.6, 139.8, 134.3, 129.2, 127.8, 117.9, 80.8, 24.6. Anal Calcd for C<sub>11</sub>H<sub>9</sub>ClO<sub>4</sub>: C, 54.90; H, 3.77. Found: C, 54.74; H, 4.08.

### EXAMPLE 5

#### 5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-propyl-2(5*H*)-furanone

- A. A total of 5.2mL (10.4mmol) of 2.0M n-propylmagnesium bromide was added to a solution of 2.4 g (10 mmol) of ethyl 4-phenylbenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to give prior to hydrogenolysis 0.30g (8% yield) of 5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-3-phenylmethoxy-5-propyl-2(5*H*)-furanone as an off white solid after crystallization from CHCl<sub>3</sub> and hexanes.
- B. Hydrogenolysis of 250 mg of 5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-3-phenylmethoxy-5-propyl-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provided 100mg (52% yield) of a white powder: mp 203-204°C dec.(acetone/CHCl<sub>3</sub>/hexanes). <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.65-7.40 (m, 9H), 2.25-1.95 (m, 2H), 1.45-1.10 (m, 2H), 0.95 (t, J=6.9Hz, 3H). Anal Calcd for C<sub>19</sub>H<sub>18</sub>O<sub>4</sub> + 0.125 H<sub>2</sub>O: C, 73.01; H, 5.88. Found: C, 72.99; H, 5.86.

### EXAMPLE 6

#### 5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-(2-methylpropyl)-2(5*H*)-furanone

A. A total of 5.2mL (10.4mmol) of 2.0M isobutylmagnesium bromide was added to a solution of 2.4 g (10 mmol) of ethyl 4-phenylbenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to give prior to hydrogenolysis 0.35g (8% yield) of 5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-3-phenylmethoxy-5-(2-methylpropyl)-2(5*H*)-furanone as an off white solid after crystallization from CHCl<sub>3</sub> and hexanes.

B. Hydrogenolysis of 350mg of 5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-3-phenylmethoxy-5-(2-methylpropyl)-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provide 190mg (69% yield) of a white powder: mp 198-199°C dec.(CHCl<sub>3</sub>/hexanes). <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.73-7.34 (m, 9H), 2.44-2.28 (m, 1H), 1.50-0.80 (m, 8H). <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 169.21, 155.47, 140.81, 139.57, 129.17, 127.73, 127.18, 127.08, 126.04, 118.47, 86.01, 40.66, 23.72, 12.11, 11.87. Anal Calcd for C<sub>20</sub>H<sub>20</sub>O<sub>4</sub> + 0.125 H<sub>2</sub>O: C, 73.55; H, 6.25. Found: C, 73.25; H, 6.36.

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#### EXAMPLE 7

##### 5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone

A. A total of 3.4mL (10.2 mmol) of 3.0M phenylmagnesium bromide was added to a solution of 2.4 g (10 mmol) of ethyl 4-phenylbenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to give prior to hydrogenolysis 0.88g (20% yield) of 5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-3-phenylmethoxy-5-phenyl-2(5*H*)-furanone as an off white solid: mp 190-195°C (CHCl<sub>3</sub>/hexanes).

B. Hydrogenolysis of 500mg of 5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-3-phenylmethoxy-5-phenyl-2(5*H*)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provide 150mg (38% yield) of 5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-phenyl-2(5*H*)-furanone as colorless needles: mp 188-191°C dec.(CHCl<sub>3</sub>/hexanes). <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.75-7.36 (m, 14H). <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 168.34, 154.84, 141.50,

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140.66, 140.30, 139.42, 129.18, 128.74, 128.59, 127.92, 127.40, 127.25, 127.07, 119.45, 84.59. Anal Calcd for  $C_{22}H_{16}O_4$ : C, 76.73; H, 4.68. Found: C, 76.44; H, 4.50.

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**EXAMPLE 8****3,4-Dihydroxy-5,5-diphenyl-2(5H)-furanone**

- A. A total of 3.5mL (10.5mmol) of 3.0M phenylmagnesium bromide was added to a solution of 1.6mL (10 mmol) of ethyl benzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5H)-furanone to give 5,5-diphenyl-4-hydroxy-3-phenylmethoxy-2(5H)-furanone as an oil, which was purified over  $SiO_2$  using acetone/hexanes (3/7).
- B. Hydrogenolysis of 5,5-diphenyl-4-hydroxy-3-phenylmethoxy-2(5H)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5H)-furanone to provide 150mg (5.6% overall yield) of 3,4-dihydroxy-5,5-diphenyl-2(5H)-furanone as colorless needles: mp 192-193 °C dec.( $CHCl_3$ /hexanes).  $^1H$  NMR (acetone- $d_6$ )  $\delta$  7.41 (s, 10H).  $^{13}C$  NMR (acetone- $d_6$ )  $\delta$  168.38, 154.92, 140.44, 128.72, 128.58, 127.43, 119.46, 84.74. Anal Calcd for  $C_{16}H_{12}O_4 + 0.25 H_2O$  C, 70.46; H, 4.62. Found: C, 70.42; H, 4.52.

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**EXAMPLE 9****3,4-Dihydroxy-5-(4-isobutylphenyl)-5-(1-propyl)-2(5H)-furanone**

- A. A total of 5.2mL (10.4mmol) of 2.0M 1-propylmagnesium bromide was added to a solution of 2.3g (10 mmol) of ethyl 4-isobutylbenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5H)-furanone to provide 4-hydroxy-5-(4-isobutylphenyl)-3-phenylmethoxy-5-(1-propyl)-2(5H)-furanone as an oil, which was purified over  $SiO_2$  using acetone/hexanes (1/4).
- B. Hydrogenolysis of 4-hydroxy-5-(4-isobutylphenyl)-3-phenylmethoxy-5-(1-propyl)-2(5H)-furanone was performed in a similar manner as described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5H)-furanone to provide 200mg,

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- (6.9% yield) of 3,4-dihydroxy-5-(4-isobutylphenyl)-5-(1-propyl)-2(5*H*)-furanone as an oil, which was purified by preparative TLC using hexanes/acetone/acetic acid (70/29/1) as eluant: <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.48-7.13 (m, 4H), 2.47 (d, *J* = 10.3 Hz, 2H), 2.10-1.66 (m, 1H), 1.29-0.85 (m, 13H). <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 169.20, 155.54, 141.58, 137.91, 129.24, 125.32, 118.25, 83.37, 45.02, 39.60, 30.26, 22.03, 16.84, 13.63. Anal Calcd for C<sub>17</sub>H<sub>22</sub>O<sub>4</sub>: C, 70.32; H, 7.64. Found: C, 70.01; H, 7.61.

### EXAMPLE 10

#### 3,4-Dihydroxy-5-(4-isobutylphenyl)-5-phenyl-2(5*H*)-furanone

- 10 A. A total of 3.5mL (10.5mmol) of 3.0M phenylmagnesium bromide was added to a solution of 2.3g (10 mmol) of ethyl 4-isobutylbenzoylformate in THF in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provide an oil, which was purified over 400g of SiO<sub>2</sub> by eluting with 500mL of CHCl<sub>3</sub>, 500mL of EtOH/CHCl<sub>3</sub> (3/97) and 500mL of EtOH/CHCl<sub>3</sub> (8/92)
- 15 to provide 1.2g (29% yield) of 4-hydroxy-5-(4-isobutylphenyl)-5-phenyl-3-phenylmethoxy-2(5*H*)-furanone as a tan powder recrystallized from CHCl<sub>3</sub> and hexanes.
- B. Hydrogenolysis of 500mg (1.2mmol) of 4-hydroxy-5-(4-isobutylphenyl)-5-phenyl-3-phenylmethoxy-2(5*H*)-furanone was performed in a similar manner as
- 20 described in the preparation of 3,4-dihydroxy-5-methyl-5-phenyl-2(5*H*)-furanone to provide 200mg (51% yield) of 3,4-dihydroxy-5-(4-isobutylphenyl)-5-phenyl-2(5*H*)-furanone as a white powder: mp 138-139 °C (CHCl<sub>3</sub>/hexanes). <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.40-7.15 (m, 9H), 2.49 (d, *J* = 7.1 Hz, 2H), 1.94-1.74 (m, 1H), 0.89 (d, *J* = 6.5 Hz, 6H). Anal Calcd for C<sub>20</sub>H<sub>20</sub>O<sub>4</sub>: C, 74.1; H, 6.2. Found: C, 73.7; H, 6.3.

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### EXAMPLE 11

#### (*S*)-(+)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone

- A. To a flame dried 500mL flask flushed with N<sub>2</sub>, was added 24g (100mmol) of ethyl 4-phenylbenzoylformate and 300mL of anhydrous THF. The solution was cooled with stirring to -25°C and 37mL (110mmol) of a 3.0M solution of methylmagnesium

iodide was added at a rate to maintain the reaction temperature below  $-10^{\circ}\text{C}$ . The reaction progress was monitored by TLC and upon disappearance of starting material, 100mL of saturated  $\text{NH}_4\text{Cl}$  solution and 200mL of ether were added. The organic layer was separated and washed with 2 x 50mL of brine, dried ( $\text{MgSO}_4$ ) and concentrated leaving racemic ethyl 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate as an oil.

B. The crude ethyl 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate was saponified by treating with 100mL of ethanol and 100mL of 4.0M NaOH solution. The suspension was stirred for 3 hours, after which a clear solution formed. The solution was concentrated, diluted with 150mL of  $\text{H}_2\text{O}$ , washed with 2 x 50mL of ether, and acidified to pH 1 with 10% HCl solution. The aqueous phase was extracted with 3 x 100mL portions of ether and the combined ether extracts were washed with 50mL of  $\text{H}_2\text{O}$ , 50mL of brine, dried ( $\text{MgSO}_4$ ) and concentrated leaving 18.3g (72% yield) of racemic 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid as a white solid after was recrystallization from  $\text{CHCl}_3$  and hexanes.

C. Racemic 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid 12.1g (50mmol) was resolved by dissolving in 225mL of a 2:2:1 mixture of isopropanol:benzene:hexanes. The solution was warmed to reflux and 6.9g (50mmol) of (*R*)-(-)-phenylglycinol was added in one portion. The mixture was allowed to cool slowly over 15 hours during which white crystals formed, which were isolated by filtration and washed with several small portions of isopropanol. The isolated white solid was recrystallized four additional times from isopropanol until a constant melting point of  $189.5\text{--}191^{\circ}\text{C}$  was observed, leaving 4.3g (45.3% yield for the resolution) of diastereomerically pure (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate (*R*)-(-)-phenylglycinol salt.

D. Diastereomerically pure (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate (*R*)-(-)-phenylglycinol salt (1.9g, 5mmol) was added to a separatory funnel containing 70mL of 15% aqueous HCl solution and 150mL of ether. The suspension was shaken until completely solvated, and the aqueous layer was separated. The ether portion was

washed with 2 x 50mL of 15% aqueous HCl solution, 50mL of H<sub>2</sub>O, 50mL of brine, dried (MgSO<sub>4</sub>) and filtered into a 500mL flask. The ether solution was cooled in an ice bath and a freshly prepared ethereal solution of diazomethane was added with stirring until the yellow color of the reagent persisted. The solution was concentrated leaving 1.3g (99%) of methyl (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate as a white crystalline material.

E. In a dry flask under argon, were mixed 1.3g (5mmol) of methyl (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate, 1.7mL (10mmol) of 95% benzyloxyacetyl chloride and 6.1mL of pyridine. The reaction stirred for 48 hours and was quenched by pouring into 100mL of 10% aqueous HCl and 200mL of ether. The ether fraction was separated and washed with 50mL of 10% aqueous HCl, 50mL of H<sub>2</sub>O, 2 x 50mL of NaHCO<sub>3</sub> solution, 50mL of H<sub>2</sub>O, 50mL of brine, dried (MgSO<sub>4</sub>) and concentrated. The product was purified over 250g of SiO<sub>2</sub> using initially EtOAc/hexanes (1/9) followed by EtOAc/hexanes (1.5/8.5) as eluant to yield 1.5g (80% yield) of methyl (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-(2-phenylmethoxyacetoyl)oxypropionate.

F. (*S*)-(+)-2-[(1,1'-Biphenyl)-4-yl]-2-(2-phenylmethoxyacetoyl)oxypropionate (1.5g, 4mmol) was dissolved in 10mL of anhydrous THF and added to 33mL of a 0.3M solution of LiHMDA in THF at -78°C. The light yellow solution stirred for 45 minutes and was quenched by the addition of 30mL of 10% aqueous HCl solution. The mixture was taken into 200mL of ether and washed with 30mL of 10% aqueous HCl solution, 30mL of H<sub>2</sub>O, 30mL of brine, dried (MgSO<sub>4</sub>) and concentrated. The resultant oil was taken up in 50mL of ether and extracted with 4 x 30mL of saturated NaHCO<sub>3</sub> solution. The combined NaHCO<sub>3</sub> fractions were washed with 25mL of ether, acidified to pH below 1 with 10% aqueous HCl solution and extracted with 2 x 100mL of ether. The combined ether extracts were washed with 25mL of H<sub>2</sub>O, 25mL of brine, dried (MgSO<sub>4</sub>) and concentrated to give (*S*)-(+)-5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-5-methyl-3-phenylmethoxy-2(5*H*)-furanone.

G. The (*S*)-(+)-5-[(1,1'-biphenyl)-4-yl]-4-hydroxy-5-methyl-3-phenylmethoxy-2(5*H*)-furanone was subjected to hydrogenation over 100 mg of 5% Pd/BaSO<sub>4</sub> in 100mL of MeOH at room temperature under 30 psi of H<sub>2</sub>. The reaction was monitored periodically by TLC analysis. Upon reaction completion, the suspension was filtered through two #1 filter papers, concentrated and recrystallized from CHCl<sub>3</sub> and hexanes to provide 300mg (20% overall yield from methyl (*S*)-(+)-2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionate) of (*S*)-(+)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone as a light weight white crystalline material: mp 204-206°C dec.; [ $\alpha$ ]<sub>D</sub><sup>25</sup> + 121° (c=0.66; MeOH); <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>)  $\delta$  7.72-7.41 (m, 9H), 1.89 (s, 3H). Anal Calcd for C<sub>17</sub>H<sub>14</sub>O<sub>4</sub> + 0.75 H<sub>2</sub>O: C, 69.03; H, 5.28. Found: C, 68.69; H, 4.95.

### EXAMPLE 12

#### (*R*)-(-)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone

A. The combined filtrates from the resolution of racemic 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid with (*R*)-(-)-phenylglycinol (example 11, section C) were concentrated to a thick brown paste and partitioned between 100mL of 20% HCl solution and 400mL of ether. The aqueous phase was separated and the ether layer was subsequently washed with 4 x 30mL of 20% HCl solution, 50mL of brine, dried (MgSO<sub>4</sub>) and concentrated. A total of 8.5g (35mmol) of 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid was recovered and dissolved in 300mL of isopropanol by warming to reflux and 4.5g (35mmol) of (*S*)-(+)-phenylglycinol was added. The diastereomeric salts were allowed to crystallize at 25°C over a period of 72 hours and isolated by filtration and washed with 2 x 40mL of isopropanol to provide 6.7g of light brown crystals. Two subsequent recrystallizations from isopropanol provided 3.6g of the diastereomerically pure salt of (*R*)-(-)- 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid with (*S*)-(+)-phenylglycinol.

B. (*R*)-(-)-5-[(1,1'-Biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone was prepared in an analogous manner as described for (*S*)-(+)-5-[(1,1'-biphenyl)-4-yl]-3,4-



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 307/62, A61K 31/34, C07D 307/91, 405/06, 417/06, 405/12, 413/12</b>		A1	(11) International Publication Number: <b>WO 98/07714</b>
			(43) International Publication Date: 26 February 1998 (26.02.98)
(21) International Application Number: <b>PCT/US97/14878</b>		(81) Designated States: AU, CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 22 August 1997 (22.08.97)			
(30) Priority Data:		Published	
60/024,440	22 August 1996 (22.08.96) US	With international search report.	
60/024,586	22 August 1996 (22.08.96) US		
08/915,099	20 August 1997 (20.08.97) US		
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(54) Title: 5-SUBSTITUTED AND 5,5-DISUBSTITUTED-3,4-DIHYDROXY-2(5H)-FURANONES AND METHODS OF USE THEREFOR			
(57) Abstract			
<p>The present invention relates to synthetic methods for the production of both optically active and racemic 5,5-disubstituted-3,4-dihydroxy-2(5H)-furanones; 5-[(4-aryl)-3-butynyl]-3,4-dihydroxy-2(5H)-furanones; 5-(2-aryltio)ethyl-3,4-dihydroxy-2(5H)-furanones; and 5-(2-aryloxy)ethyl-3,4-dihydroxy-2(5H)-furanones. This invention further relates to the use of the above mentioned compounds as anti-inflammatory agents through their action as mixed inhibitors of lipid peroxidation, 5-lipoxygenase, cyclooxygenase-1 and cyclooxygenase-2. The invention further relates to the use of such compounds in the treatment of chronic inflammatory disorders such as asthma, rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, acute respiratory distress syndrome, and central nervous system disorders such as Alzheimer's and Parkinson's diseases wherein reactive oxygen species and inflammatory mediators are contributing deleterious factors.</p>			

dihydroxy-5-methyl-2(5*H*)-furanone starting with 1.9g (5.0mmol) of the diastereomerically pure salt of (*R*)-(-)- 2-[(1,1'-biphenyl)-4-yl]-2-hydroxypropionic acid and (*S*)-(+)-phenylglycinol to provide 280mg (19% yield) of (*R*)-(-)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone as a white crystalline material: mp 197-199 °C dec. (CHCl<sub>3</sub>/hexanes); [ $\alpha$ ]<sub>D</sub><sup>25</sup> -182° (c=1.42; MeOH); <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>)  $\delta$  7.65-7.41 (m, 9H), 1.89 (s, 3H). Anal Calcd for C<sub>17</sub>H<sub>14</sub>O<sub>4</sub> + 0.25 H<sub>2</sub>O: C, 71.20; H, 5.10. Found: C, 71.19; H, 4.74.

### EXAMPLE 13

10 (*R*)-(-)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone  
(*R*)-(-)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone was synthesized in an analogous manner used for the production of (*S*)-(+)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone starting with ethyl 4-isobutylbenzoylformate. (*R*)-(-)-Phenylglycinol was used to resolve the methyl (*R*)-(-)-2-(4-isobutylphenyl)propionate enantiomer, of which 1.2g, (5mmol) was converted into 190mg (15% yield) of (*R*)-(-)-3,4-dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone as a white crystalline material: mp 180-181 °C dec. (CHCl<sub>3</sub>/hexanes); [ $\alpha$ ]<sub>D</sub><sup>25</sup> -137° (c=1.27; MeOH); <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>)  $\delta$  7.44-7.14 (m, 4H), 2.48 (d, 2H, J = 7.1 Hz), 1.87-1.82 (m, 1H), 1.83 (s, 3H), 0.88 (d, 6H, J = 6.5 Hz). Anal Calcd for C<sub>15</sub>H<sub>18</sub>O<sub>4</sub>: C, 68.68; H, 6.92. Found: C, 68.52; H, 7.01.

### EXAMPLE 14

(*S*)-(+)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone  
(*S*)-(+)-3,4-Dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone was synthesized in an analogous manner used for the production of (*R*)-(-)-5-[(1,1'-biphenyl)-4-yl]-3,4-dihydroxy-5-methyl-2(5*H*)-furanone starting with ethyl 4-isobutylbenzoylformate. (*S*)-(+)-Phenylglycinol was used to resolve the methyl (*S*)-(+)-2-(4-isobutylphenyl)propionate enantiomer, of which 1.2g (5mmol) was converted into 250mg (19% yield) of (*S*)-(+)-3,4-dihydroxy-5-methyl-5-[4-(2-methylpropyl)phenyl]-2(5*H*)-furanone as a white crystalline material: mp 175-177 °C

dec. (CHCl<sub>3</sub>/hexanes); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +132° (c=1.55; MeOH) <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>)  $\delta$  7.44-7.14 (m, 4H), 2.48 (d, 2H, J = 7.1 Hz), 1.87-1.82 (m, 1H), 1.83 (s, 3H), 0.88 (d, 6H, J = 6.5 Hz). Anal Calcd for C<sub>15</sub>H<sub>18</sub>O<sub>4</sub>: C, 68.68; H, 6.92. Found: C, 68.08; H, 6.90.

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### EXAMPLE 15

#### 3,4-Dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone

A. A mixture consisting of 340mg (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone, 320mg (1.3mmol) of triphenylphosphine and 225mg (1.2mmol) of 4-phenoxyphenol was dissolved in 8mL of anhydrous THF under argon. Diisopropyl azodicarboxylate (276 $\mu$ L 1.4mmol) was added to the solution dropwise with stirring at 25°C. After 36 hours the reaction mixture was poured into 30mL of H<sub>2</sub>O and extracted with two 30mL portions of ether. The combined ether fractions were washed with 25mL of saturated NaHCO<sub>3</sub> solution, 25mL of H<sub>2</sub>O, 25mL of aqueous 10% HCl solution, 25mL of H<sub>2</sub>O, 25mL of brine, dried (MgSO<sub>4</sub>) and concentrated to an oil. The product was purified over silica gel using EtOAc/hexanes (2/3) as eluant to provide 3,4-dibenzyloxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone as an oil.

B. The 3,4-dibenzyloxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone was hydrogenated in 50mL of MeOH over 50mg of 5% Pd/BaSO<sub>4</sub> under 30psi H<sub>2</sub>. After completion of the reaction, as determined by TLC analysis, the suspension was filtered through celite, washed with three 10mL portions of MeOH and concentrated to a white solid. Trituration with ether and hexanes provided 150mg (44% yield) of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone as a white powder: mp 125-127 °C, <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>)  $\delta$  7.42-7.28 (m, 2H), 7.12-6.88 (m, 7H), 4.95 (dd, 1H), 4.17 (q<sub>ab</sub>, 2H), 2.55-2.36 (m, 1H), 2.05-1.87 (m, 1H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>)  $\delta$  169.41, 158.91, 155.57, 153.39, 150.61, 129.98, 122.73, 120.94, 117.71, 116.32, 115.99, 72.43, 63.97, 32.43; Anal Calcd for C<sub>18</sub>H<sub>16</sub>O<sub>6</sub> + 0.5 H<sub>2</sub>O; C, 64.12; H, 5.04: Found C, 64.28; H, 5.04.

**EXAMPLE 16****3,4-Dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5H)-furanone**

Mitsunobu coupling of 0.33g (1.4mmol) of 6-hydroxyflavone with 0.40g (1.17mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5H)-furanone and subsequent benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5H)-furanone to provide 3,4-dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5H)-furanone as a tan solid: mp 200-220°C dec. (acetone/hexanes), <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.13-7.36 (m, 8H), 7.01 (s, 1H), 4.92 (dd, 1H), 4.17 (t, 2H), 2.47-2.27 (m, 1H), 1.98-1.85 (m, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 177.23, 170.22, 162.71, 156.02, 155.36, 150.80, 132.06, 131.51, 129.42, 126.59, 124.31, 123.85, 120.49, 117.44, 106.43, 105.85, 72.24, 64.20, 31.71. Anal Calcd for C<sub>21</sub>H<sub>16</sub>O<sub>7</sub> + 0.25 H<sub>2</sub>O: C, 65.55; H, 4.44. Found: C, 65.59; H, 4.49.

**EXAMPLE 17****5-[2-(Dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5H)-furanone**

Mitsunobu coupling of 0.22g (1.2mmol) of 2-hydroxydibenzofuran with 0.34g (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5H)-furanone and subsequent benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5H)-furanone to provide 40 mg (10% yield) of 5-[2-(dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5H)-furanone a white solid: mp 191-192°C (ether/hexanes), <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 8.23-8.18 (m, 1H), 7.83-7.44 (m, 5H), 7.28-7.23 (m, 1H), 5.12 (dd, J=5.3, 8.7Hz, 1H), 4.42 (dd, J=2.6, 4.7Hz, 2H), 2.69-2.59 (m, 1H), 2.21-2.08 (m, 1H). <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 169.68, 157.31, 155.75, 153.70, 151.31, 127.76, 125.05, 124.83, 123.07, 121.34, 118.46, 116.42, 112.39, 111.90, 105.40, 72.72, 64.57, 32.64. Anal Calcd for C<sub>18</sub>H<sub>14</sub>O<sub>6</sub> + 0.25 H<sub>2</sub>O: C, 65.36; H, 4.57. Found: C, 65.52; H, 4.23.



**EXAMPLE 18****3,4-Dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5H)-furanone**

Mitsunobu coupling of 0.17g (1.2mmol) of 1-naphthol with 0.34g (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5H)-furanone and subsequent benzyl group  
5 deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5H)-furanone to provide 75mg (26% yield) of 3,4-dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5H)-furanone as colorless cubes: mp 163-164°C (ether/hexanes) <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 8.38-8.25 (m, 1H), 7.92-7.79 (m, 1H), 7.60-7.34 (m, 4H), 7.05-6.93 (m, 1H), 5.11 (dd, J=5.3, 8.7Hz,  
10 1H), 4.39 (dd, J=2.6, 4.7Hz, 2H), 2.75-2.52 (m, 1H), 2.25-2.05 (m, 1H). <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 169.62, 154.92, 153.61, 135.13, 127.83, 126.78, 126.50, 125.92, 125.05, 122.41, 120.66, 118.53, 105.28, 72.85, 63.93, 32.58. Anal Calcd for C<sub>16</sub>H<sub>14</sub>O<sub>5</sub>: C, 67.11; H, 4.89. Found: C, 66.70; H, 4.88.

**EXAMPLE 19****3,4-Dihydroxy-5-[2-(1,8-naphthalimide)-N-ethyl]-2(5H)-furanone**

Mitsunobu coupling of 0.24g (1.2mmol) of 1,8-naphthalimide with 0.34g (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5H)-furanone and subsequent benzyl group  
deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5H)-furanone to provide  
20 150mg (45% yield) of 3,4-dihydroxy-5-[2-(1,8-naphthalimide)-N-ethyl]-2(5H)-furanone as a white powder: mp 235-250°C dec. (acetone/hexanes), <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.62-8.35 (m, 4H), 7.92-7.82 (m, 2H), 4.82 (dd, J=5.3, 8.7Hz, 1H), 4.19 (t, J=4.2Hz, 2H), 2.32-2.16 (m, 1H), 1.90-1.75 (m, 1H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 170.29, 163.72, 154.91, 134.56, 131.52, 130.96, 127.60, 127.45, 122.29, 117.46,  
25 73.64, 36.03, 30.58. Anal Calcd for C<sub>18</sub>H<sub>13</sub>NO<sub>6</sub>: C, 63.71; H, 3.86; N, 4.12. Found: C, 63.84; H, 3.83; N, 4.00.

**EXAMPLE 20****3,4-Dihydroxy-5-[2-(1,8-naphthosultam)-*N*-ethyl]-2(5*H*)-furanone**

Mitsunobu coupling of 0.28g (1.3mmol) of 1,8-naphthosultam with 0.37g (1.1mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent benzyl group  
5 deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone to provide 100mg (29% yield) of 3,4-dihydroxy-5-[2-(1,8-naphthosultam)-*N*-ethyl]-2(5*H*)-furanone as a light yellow powder: mp 85-95°C dec. (acetone/hexanes), <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 8.29-7.55 (m, 5H), 7.12-7.01 (m, 1H), 4.97 (dd, J=4.9, 8.7Hz, 1H), 4.10  
10 (t, J=4.2Hz, 2H), 2.72-2.50 (m, 1H), 2.18-1.95 (m, 1H). <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 169.28, 152.93, 136.42, 131.65, 131.10, 130.84, 130.00, 128.82, 120.03, 119.10, 118.60, 118.42, 103.71, 73.01, 37.72, 31.45. Anal Calcd for C<sub>16</sub>H<sub>13</sub>NO<sub>6</sub>S + 1H<sub>2</sub>O: C, 52.60; H, 4.14; N, 3.83. Found: C, 52.62; H, 3.86; N, 3.56.

**EXAMPLE 21****3,4-Dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5*H*)-furanone**

Mitsunobu coupling of 0.28g (1.3mmol) of 2-hydroxy diphenylmethane with 0.37g (1.1mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-  
20 furanone to provide 140mg (43% yield) of 3,4-dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5*H*)-furanone as a white powder, which was purified by trituration with ether and hexanes: <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.33-6.82 (m, 9H), 4.78 (dd, J=5.3, 8.7Hz, 1H), 4.19 (dd, J=2.6, 4.7Hz, 2H), 3.96 (s, 2H); 2.57-2.36 (m, 1H), 2.10-1.82 (m, 1H). Anal Calcd for C<sub>19</sub>H<sub>18</sub>O<sub>5</sub>: C, 69.9; H, 5.6. Found: C, 69.75; H, 5.52.

25

**EXAMPLE 22****5-[2-((1,1'-Biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone**

Mitsunobu coupling of 0.20g (1.2mmol) of 4-hydroxy-1,1'-biphenyl with 0.34g (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent

benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone to provide 100mg (32% yield) of 5-[2-((1,1'-biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone as a white powder after trituration with ether and hexanes:

- 5 <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.71-7.02 (m, 9H), 4.97 (dd, *J*=4.9, 8.7Hz, 1H), 4.25 (dd, *J*=2.6, 4.7Hz, 2H), 2.58-2.41 (m, 1H), 2.10-1.92 (m, 1H). Anal Calcd for C<sub>18</sub>H<sub>16</sub>O<sub>5</sub> + 1H<sub>2</sub>O: C, 67.49; H, 5.66. Found: C, 67.34; H, 5.42.

### EXAMPLE 23

#### 3,4-Dihydroxy-5-[2-(quinoline-2-oxy)ethyl]-2(5*H*)-furanone

- 10 Mitsunobu coupling of 0.17g (1.2mmol) of 2-hydroxyquinoline with 0.34g (1.0mmol) of 3,4-dibenzyloxy-5-(2-hydroxyethyl)-2(5*H*)-furanone and subsequent benzyl group deprotection by hydrogenation were performed in a similar manner as described in the synthesis of 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5*H*)-furanone to provide 50mg (17% yield) of 3,4-dihydroxy-5-[2-(quinoline-2-oxy)ethyl]-
- 15 2(5*H*)-furanone as a fluffy white solid after recrystallization from ether and hexanes: <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 8.25-8.17 (m, 1H); 7.88-7.38 (m, 4H), 7.01-6.93 (m, 1H); 4.97 (dd, *J*=4.9, 8.7Hz, 1H), 4.81-4.55 (m, 2H); 2.62-2.45 (m, 1H), 2.20-1.95 (m, 1H). Anal Calcd for C<sub>15</sub>H<sub>13</sub>NO<sub>5</sub> + 0.5H<sub>2</sub>O: C, 60.81; H, 5.10; N, 4.72. Found: C, 61.04; H, 5.04; N, 4.32.

20

### EXAMPLE 24

#### 3,4-Dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone

- A suspension of 3.14g (12.4mmol) 4,5-diphenyl-2-thio-1,3-isoxazole in 12mL of THF under argon with stirring at -78°C was treated with 4.9mL (12.2mmol) of 2.5M *n*BuLi. The reaction mixture was warmed to -5°C and 1.1g (4mmol) of 3,4-
- 25 dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone dissolved in 12mL of HMPA was added at a rate to maintain the reaction temperature below 0°C. Stirring continued at 0 to -5°C for 60 minutes followed by the addition of 100mL of saturated NH<sub>4</sub>Cl solution. The mixture was extracted with 2 x 100 mL portions of ether/EtOAc (1/1). The organic

fractions were combined and extracted with 3 x 50 mL of saturated NaHCO<sub>3</sub> solution. The bicarbonate extracts were combined, washed with 2 x 50mL of ether, acidified to pH 1 with 10% HCl solution and extracted into 2 x 100mL portions of ether. The ether extracts were combined and washed successively with 40mL of H<sub>2</sub>O, 40mL of  
5 brine, dried (MgSO<sub>4</sub>) and concentrated to an oil.

Purification over SiO<sub>2</sub> using acetone/hexanes (1:1 to 2:3 to 7:3) provided a brown colored solid upon evaporation of solvent. The solid was taken up in 100mL of ether and extracted with 3 x 50mL of NaHCO<sub>3</sub> solution. The combined aqueous  
10 extracts were acidified with 10% HCl solution and extracted with 2 x 100mL portions of ether. The organic portions were washed with 40mL of H<sub>2</sub>O, 40mL of brine, dried (MgSO<sub>4</sub>) and concentrated to provide 875mg (55% yield) of 3,4-dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone as a white foam: mp 88-91 °C, <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.67-7.39 (m, 10H), 4.95 (dd, J=3.7, 8.7Hz, 1H), 3.61-3.28 (m, 2H), 2.72-2.19 (m, 2H). <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 169.17, 159.13, 152.70, 147.65,  
15 136.83, 132.60, 129.14 (2C), 128.85 (2C), 128.61, 128.11, 126.92, 118.91, 74.25, 32.69, 27.32. Anal Calcd for C<sub>21</sub>H<sub>17</sub>NO<sub>5</sub>S + 0.25 H<sub>2</sub>O: C, 63.07; H, 4.41; N, 3.50. Found: C, 63.23; H, 4.70; N, 3.24.

### EXAMPLE 25

#### 3,4-Dihydroxy-5-[2-(naphthyl-1-thio)ethyl]-2(5*H*)-furanone

20 1-Naphthalenethiol (430μL, 3.1mmol) and 0.27g (1mmol) of 3,4-dihydroxy-5-(2-iodoethyl)-2(5*H*)-furanone were reacted in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5*H*)-furanone to provide 90mg (30% yield) of 3,4-dihydroxy-5-[2-(naphthyl-1-thio)ethyl]-2(5*H*)-furanone as a colorless oil. Additional purification by chromatography over  
25 SiO<sub>2</sub> was not necessary for this compound: <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 8.44-8.32 (m, 1H), 7.98-7.43 (m, 6H), 4.92 (dd, J=3.7, 8.7Hz, 1H), 3.28-3.06 (m, 2H), 2.39-2.19 (m, 1H), 2.02-1.84 (m, 1H). Anal Calcd for C<sub>16</sub>H<sub>14</sub>O<sub>4</sub>S + 0.25 H<sub>2</sub>O: C, 62.63; H, 4.76. Found: C, 63.06; H, 5.19.

**EXAMPLE 26****3,4-Dihydroxy-5-[2-(naphthyl-2-thio)ethyl]-2(5H)-furanone**

2-Naphthalenethiol (430  $\mu$ L, 3.1 mmol) and 0.27 g (1 mmol) of 3,4-dihydroxy-5-(2-iodoethyl)-2(5H)-furanone were reacted in an analogous manner as described for the synthesis of 3,4-dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5H)-furanone to provide 140 mg (46% yield) of 3,4-dihydroxy-5-[2-(naphthyl-2-thio)ethyl]-2(5H)-furanone as a white powder after trituration with ether and hexanes. Additional purification by chromatography over  $\text{SiO}_2$  was not necessary for this compound:  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  7.95-7.82 (m, 4H), 7.58-7.40 (m, 3H), 4.92 (dd,  $J=3.7, 8.7\text{Hz}$ , 1H), 3.34-3.08 (m, 2H), 2.42-2.21 (m, 1H), 2.02-1.86 (m, 1H).  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  169.53, 153.03, 134.48, 134.09, 132.29, 128.99, 128.13, 127.49, 127.41, 127.08, 126.65, 126.14, 118.68, 74.25, 32.33, 27.81. Anal Calcd for  $\text{C}_{16}\text{H}_{14}\text{O}_4\text{S}$ : C, 63.56; H, 4.67. Found: C, 63.44; H, 4.58.

**EXAMPLE 27****3,4-Dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5H)-furanone**

To a flame dried reaction flask fitted with an argon inlet, septum and magnetic stir bar, were added 58 mg (0.05 mmol) of  $\text{Pd}(\text{PPh}_3)_4$ , 225  $\mu$ L (2.0 mmol) of iodobenzene, 0.17 g (1.0 mmol) of 5-(3-butynyl)-3,4-dihydroxy-2(5H)-furanone, 2 mL of pyrrolidine and 20 mg (0.10 mmol) of copper (I) iodide. The flask was protected from light (foil) and the yellow mixture was stirred at room temperature until the starting 5-(3-butynyl)-3,4-dihydroxy-2(5H)-furanone was not visible by TLC analysis ( $\text{CHCl}_3:\text{MeOH}$  9:1). The reaction mixture was poured into a mixture of 50 g of ice and 10 mL of 37% HCl, and extracted with 2 x 50 mL of ether. The ether extracts were combined and washed with 2 x 20 mL of 10% aqueous HCl solution. 20 mL of  $\text{H}_2\text{O}$ , 20 mL of brine, dried ( $\text{MgSO}_4$ ) and concentrated.

The residue was dissolved in 30 mL of ether and extracted with 3 x 15 mL of saturated  $\text{NaHCO}_3$  solution. The bicarbonate extracts were pooled and washed with 10 mL of ether, acidified to pH 2 with 10% HCl solution and extracted with 2 x 25 mL of ether.

The ether extracts were combined and washed with 10mL of H<sub>2</sub>O, 3mL of 10% (w/w) NaHCO<sub>3</sub> solution, 10mL of H<sub>2</sub>O, 10mL of brine, dried (MgSO<sub>4</sub>) and concentrated to provide 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone as a white solid: mp 145-146°C; <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.35-7.15 (m, 5H) 4.75 (dd, J=3.4, 8.2 Hz, 1H), 2.50-2.40 (m, 2H), 2.20-2.05 (m, 1H), 1.75-1.60 (m, 1H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 170.2, 153.8, 132.3, 129.2, 128.7, 124.6, 119.0, 89.3, 82.1, 74.9, 32.4, 15.3.

### EXAMPLE 28

#### 3,4-Dihydroxy-5-[(4-(2-methyl)phenyl)-3-butynyl]-2(5*H*)-furanone

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (0.17g, 1.0mmol) and 256μL (2.0 mmol) of 2-iodotoluene were coupled in an analogous fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using CHCl<sub>3</sub>/MeOH (96/4) as eluant to provide 3,4-dihydroxy-5-[(4-(2-methyl)phenyl)-3-butynyl]-2(5*H*)-furanone as a light yellow solid: mp 111-112°C, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.37-7.07 (m, 4H), 5.01 (dd, J=3.5, 8.5 Hz, 1H), 2.69-2.65 (m, 2H), 2.40 (s, 3H), 2.39-2.27 (m, 1H), 1.97-1.86 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.6, 155.8, 140.0, 131.9, 129.3, 127.9, 125.5, 123.1, 117.5, 91.5, 80.9, 76.4, 31.3, 20.7, 15.3; Anal Calcd for C<sub>15</sub>H<sub>14</sub>O<sub>4</sub>: C, 69.76; H, 5.46. Found: C, 69.41; H, 5.58.

### EXAMPLE 29

#### 3,4-Dihydroxy-5-[(4-(2-(2*Z*-hexenyl))phenyl)-3-butynyl]-2(5*H*)-furanone

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (0.34g, 2.0mmol) and 1.1g (4.0 mmol) of 2-(2*Z*-hexenyl)iodobenzene were coupled in an analogous fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using CHCl<sub>3</sub>/MeOH (96/4) as eluant and dried at 0.05 mm Hg at 58°C for 2h to provide 100 mg (17% yield) of 3,4-dihydroxy-5-[(4-(2-(2*Z*-hexenyl))phenyl)-3-butynyl]-2(5*H*)-furanone as a yellow oil: <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.43-7.15 (m, 4H), 5.70-5.45 (m, 2H), 4.91 (dd, 1H, J = 3.4, 8.3 Hz), 3.57 (d, 2H, J =

5.9 Hz), 2.66 (t, 2H,  $J = 7.0$  Hz), 2.37-2.11 (m, 3H), 2.00-1.85 (m, 1H), 1.48-1.29 (m, 2H), 0.93 (t, 3H,  $J = 7.3$  Hz); Anal Calcd for  $C_{20}H_{22}O_4 + 0.2 H_2O$ : C, 72.80; H, 6.84. Found: C, 72.99; H, 6.96.

5

**EXAMPLE 30**

**3,4-Dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5H)-furanone**  
5-(3-Butynyl)-3,4-dihydroxy-2(5H)-furanone (0.12g, 0.71 mmol) and 0.35g (1.1mmol) of 2-(phenylthio)methyl-1-iodobenzene were coupled in an analogous fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-  
10 2(5H)-furanone. The residue was purified over silica gel using  $CHCl_3/MeOH/AcOH$  (96/3/1) as eluant and dried at 0.05 mm Hg at 58°C for 2h to provide 180 mg (69%) of 3,4-dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5H)-furanone a light yellow oil:  $^1H$  NMR (acetone- $d_6$ )  $\delta$  7.44-7.19 (m, 9H), 4.90 (dd,  $J=3.3, 8.3$  Hz, 1H), 4.36 (s, 2H), 2.63 (t,  $J=7.6$  Hz, 2H), 2.28-2.21 (m, 1H), 1.90-1.81 (m, 1H); Anal  
15 Calcd for  $C_{21}H_{18}O_4S$ : C, 68.85; H, 4.95. Found: C, 68.63; H, 5.11.

**EXAMPLE 31**

**3,4-Dihydroxy-5-[(4-(2-phenylsulfonamide-(N-butyl))-3-butynyl)-2(5H)-furanone**  
5-(3-Butynyl)-3,4-dihydroxy-2(5H)-furanone (0.17g, 1.0 mmol) and 400mg (1.2mmol) of N-butyl-2-iodobenzenesulfonamide were coupled in an analogous  
20 fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5H)-furanone. The residue was purified over silica gel using  $CHCl_3/MeOH/AcOH$  (500/16/0.5) as eluant and dried at 0.05mm Hg at 58°C for 2h to provide 3,4-dihydroxy-5-[(4-(2-phenylsulfonamide-(N-butyl))-3-butynyl]-2(5H)-furanone as a light yellow oil:  $^1H$  NMR (acetone- $d_6$ )  $\delta$  8.00-7.96 (m, 1H), 7.59-7.55 (m, 1H), 7.33-  
25 7.24(m, 2H), 6.66(s, 1H), 4.82 (dd,  $J=3.4, 8.3$  Hz, 1H), 3.44-3.36 (m, 2H), 3.23-3.14 (m, 2H), 2.52-2.45 (m, 1H), 2.00-1.94 (m, 1H), 1.69-1.53 (m, 2H), 1.43-1.29 (m, 2H), 0.81 (t,  $J=7.2$  Hz, 3H);  $^{13}C$  NMR (acetone- $d_6$ )  $\delta$  169.8, 153.5, 141.6, 137.6, 130.0, 124.2, 123.8, 120.9, 118.6, 114.4, 108.7, 74.8, 53.6, 32.0, 24.9, 24.1, 20.9, 12.9; Anal Calcd for  $C_{18}H_{21}NO_6S$ : C, 56.99; H, 5.58; N, 3.69. Found: C, 56.71; H, 5.65; N, 3.48.

**EXAMPLE 32**

**3,4-Dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5*H*)-furanone**  
5 5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (0.17g, 1.0 mmol) and 300μL  
(2.0mmol) of 2-iodonaphthalene were coupled in an analogous fashion as described  
for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The  
residue was purified over silica gel using CHCl<sub>3</sub>/MeOH/AcOH (96/3/1) as eluant and  
dried at 0.05mm Hg at 58°C for 2h to provide 230 mg (75%) of 3,4-dihydroxy-5-[4-  
(2-naphthyl)-3-butynyl]-2(5*H*)-furanone as a yellow wax: <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ  
10 8.4-8.3 (m, 1H), 7.96-7.88 (m, 2H), 7.70-7.43 (m, 4H), 4.98 (dd, J=3.4, 8.3 Hz, 1H),  
2.82-2.75 (m, 2H), 2.48-2.29 (m, 1H), 2.00-1.85 (m, 1H); Anal Calcd for C<sub>18</sub>H<sub>14</sub>O<sub>4</sub> +  
0.5 H<sub>2</sub>O: C, 71.27; H, 4.98. Found: C, 71.33; H, 4.87.

**EXAMPLE 33**

**3,4-Dihydroxy-5-[(4-(2-(propylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone**  
15 5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (0.17g, 1.0 mmol) and 440mg  
(1.5mmol) of 2-(propylthio)methyl-iodobenzene were coupled in an analogous  
fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-  
2(5*H*)-furanone. The residue was purified over silica gel using CHCl<sub>3</sub>/MeOH/AcOH  
(500/16/0.5) as eluant and dried at 0.05mm Hg at 58°C for 2h to provide 240 mg  
20 (72% yield) of 3,4-dihydroxy-5-[(4-(2-(propylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-  
furanone as a yellow oil: <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.44-7.21 (m, 4H), 4.90 (dd, J=3.4,  
8.3 Hz, 1H), 3.89 (s, 2H), 2.70-2.63 (m, 2H), 2.48-2.41 (m, 2H), 2.26-2.21 (m, 1H),  
1.90-1.81 (m, 1H) 1.64-1.53 (m, 2H), 0.93 (t J=7.3 Hz, 3H); Anal Calcd for  
C<sub>18</sub>H<sub>20</sub>O<sub>4</sub>S: C, 65.05; H, 6.07. Found: C, 64.51; H, 6.28.

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**EXAMPLE 34**

**3,4-Dihydroxy-5-[(4-(2-(1-pentylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone**  
5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (84mg, 0.5 mmol) and 240mg  
(0.75mmol) of 2-(methyl-1-pentylsulfide)iodobenzene were coupled in an analogous



fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using CHCl<sub>3</sub>/MeOH/AcOH (500/16/0.5) as eluant and dried at 0.05mm Hg at 58°C for 2hours to provide 3,4-dihydroxy-5-[(4-(2-(pentylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone: <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.43-7.21 (m, 4H), 4.95 (dd, J=3.4, 8.4 Hz, 1H), 3.89 (s, 2H), 2.70-2.63 (m, 2H), 2.50-2.43 (m, 2H), 2.26-2.21 (m, 1H), 2.00-1.81 (m, 1H) 1.66-1.45 (m, 2H), 1.43-1.20 (m, 4H), 0.87 (t, J=7.2 Hz, 3H); Anal Calcd for C<sub>20</sub>H<sub>24</sub>O<sub>4</sub>S + 0.5 H<sub>2</sub>O: C, 65.02; H, 6.82. Found: C, 65.38; H, 6.69.

10

**EXAMPLE 35****3,4-Dihydroxy-5-[(4-(2-(propylsulfonyl)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone**

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (236mg, 1.2 mmol) and 600mg (1.5mmol) of 2-methyl-(1-propylsulfone)iodobenzene were coupled in an analogous fashion as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using CHCl<sub>3</sub>/MeOH/AcOH (500/16/0.5) as eluant and dried at 0.05mm Hg at 58°C for 2h to provide 250 mg (50% yield) of 3,4-dihydroxy-5-[(4-(2-(propylsulfonyl)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone as a light yellow oil: <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.56-7.34 (m, 4H), 4.96 (dd, J=3.4, 8.2 Hz, 1H), 4.57 (s, 2H), 3.03-2.95 (m, 2H), 2.71-2.64 (m, 2H), 2.35-2.26 (m, 1H), 1.94-1.70 (m, 3H), 1.02 (t, J=7.4 Hz, 3H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 169.9, 153.5, 132.9, 132.1, 131.0, 128.9, 128.5, 125.3, 118.6, 94.0, 79.6, 74.4, 57.2, 54.0, 31.5, 15.7, 14.8, 12.7; Anal Calcd for C<sub>18</sub>H<sub>20</sub>O<sub>6</sub>S: C, 59.34; H, 5.53. Found: C, 58.93; H, 5.76.

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**EXAMPLE 36****3,4-Dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5*H*)-furanone**

5-(3-Butynyl)-3,4-dihydroxy-2(5*H*)-furanone (750mg, 4.5mmol) and 2.6g (8.2mmol) of 4-(4-fluorophenylmethyl)-2-iodothiophene were coupled in an analogous fashion as

described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone. The residue was purified over silica gel using CHCl<sub>3</sub>/MeOH/AcOH (500/15/0.5) as eluant and dried at 0.05mm Hg at 58°C for 2h to provide 1.2g (75% yield) of 3,4-dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5*H*)-furanone as a brown wax: mp 119-121°C <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>) δ 7.38-7.25 (m, 2H), 7.13-6.99 (m, 3H), 6.78-6.74 (m, 1H), 4.84 (dd, J=3.3, 8.1 Hz, 1H), 4.14 (s, 2H), 2.59 (t, J=7.1 Hz, 2H), 2.38-2.14 (m, 1H), 1.90-1.69 (m, 1H); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>) δ 169.19, 164.04, 157.29, 152.78, 145.79, 136.74, 131.80, 130.80, 130.47, 125.54, 122.74, 118.84, 115.89, 115.03, 92.44, 74.90, 74.31, 35.14, 31.84, 15.02; Anal Calcd for C<sub>19</sub>H<sub>15</sub>FO<sub>4</sub>S: C, 63.69; H, 4.22. Found: C, 63.42; H, 4.33.

### EXAMPLE 37

#### 3,4-Dihydroxy-5-(4-phenylbutanyl)-2(5*H*)-furanone

Quinoline (70 μL, 0.6 mmol), 15mg of 5% Pd/BaSO<sub>4</sub> and 61mg (0.25mmol) of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone were combined in 20mL of ethanol and hydrogenated at atmospheric pressure until 12 mL (0.5mmol) of H<sub>2</sub> was consumed as measured by a H<sub>2</sub>O filled burette. The catalyst was removed by filtration through two #1 fluted filter papers and the solution was concentrated to a volume of about 5mL, taken up in 50mL of ether and washed with 3 x 15mL of 5% aqueous HCl, 20mL of H<sub>2</sub>O and 20mL of brine, dried (MgSO<sub>4</sub>) and concentrated to provide 3,4-dihydroxy-5-(4-phenylbutanyl)-2(5*H*)-furanone as a brown wax: <sup>1</sup>H NMR (acetone- *d*<sub>6</sub>) δ 7.28-7.13 (m, 5H), 4.66 (dd, J=3.4, 7.2 Hz, 1H), 2.62 (t, J=7.7, 2H), 2.00-1.93 (m, 1H), 1.69-1.42 (m, 5H); <sup>13</sup>C NMR (acetone- *d*<sub>6</sub>) δ 170.7, 154.9, 143.3, 129.2, 129.1, 126.5, 118.6, 76.2, 36.3, 32.7, 32.1, 24.6. Anal Calcd for C<sub>14</sub>H<sub>16</sub>O<sub>4</sub> + 0.25 H<sub>2</sub>O: C, 66.52; H, 6.58. Found: C, 66.71; H, 6.75.

### EXAMPLE 38

#### 3,4-Dihydroxy-5-[(4-phenyl)-3*Z*-butenyl]-2(5*H*)-furanone

Quinoline (70 μL, 0.6 mmol), 15mg of 5% Pd/BaSO<sub>4</sub> and 62mg (0.25mmol) of 3,4-dihydroxy-5-[(4-phenyl)-3-butynyl]-2(5*H*)-furanone were combined in 20mL of

ethanol and hydrogenated at atmospheric pressure until 6 mL (0.25mmol) of H<sub>2</sub> was consumed as measured by a H<sub>2</sub>O filled burette. The catalyst was removed by filtration through 2 fluted filter papers and the solution was concentrated, taken up in 50mL of ether and washed with 3 x 15mL of 5% aqueous HCl, 20mL of H<sub>2</sub>O and 5 20mL of brine, dried (MgSO<sub>4</sub>) and concentrated to give 3,4-dihydroxy-5-[(4-phenyl)-3Z-butenyl]-2(5H)-furanone as the major constituent in a mixture of alkyne, cis alkene and alkane (1.0/5.0/0.5) as determined by <sup>1</sup>H NMR spectra: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.34-7.14 (m, 5H), 6.46 (d, J=11.5 Hz, 1H), 5.65-5.57 (m, 1H), 4.77 (dd, 3.5, 8.0 Hz, 1H), 2.49 (dd, J<sub>ab</sub>=7.6 Hz, 2H), 2.16-2.09 (m, 1H), 1.80-1.70 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 10 173.4, 155.9, 137.1, 130.4, 130.3, 128.7, 128.3, 128.3, 126.8, 117.5, 77.2, 31.8, 23.5.

### EXAMPLE 39

#### 3,4-Dihydroxy-5[(4-(2-methyl)phenyl)-3Z-butenyl]-2(5H)-furanone

3,4-Dihydroxy-5[(4-(2-methyl)phenyl)-3-butyne]-2(5H)-furanone (65mg, 0.25mmol) was reduced in a similar manner as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3Z-butenyl]-2(5H)-furanone to produce 3,4-dihydroxy-5[(4-(2-methyl)phenyl)-3Z-butenyl]-2(5H)-furanone as an oil consisting of only the cis isomer as observed by the <sup>1</sup>H NMR spectra. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.34-7.20 (m, 4H), 6.59 (d, J=11.4 Hz, 1H), 5.81-5.73 (m, 1H), 4.81 (dd, J=3.4, 8.2 Hz, 1H), 2.49-2.35 (m, 2H), 2.33 (s, 3H), 2.17-2.13 (m, 1H), 1.81-1.75 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 173.6, 156.0, 20 136.2, 136.2, 130.2, 129.9, 129.6, 128.8, 127.1, 125.5, 117.4, 77.3, 31.9, 23.4, 19.9.

### EXAMPLE 40

#### 3,4-Dihydroxy-5[(4-(2-(2Z-hexenyl))phenyl)-3Z-butenyl]-2(5H)-furanone

3,4-Dihydroxy-5[(4-(2-(2-hexynyl))phenyl)-3Z-butenyl]-2(5H)-furanone (75mg, 0.25mmol) was reduced in a similar manner as described for the synthesis of 3,4-dihydroxy-5-[(4-phenyl)-3Z-butenyl]-2(5H)-furanone to produce 3,4-dihydroxy-5[(4-(2-(2Z-hexenyl))phenyl)-3Z-butenyl]-2(5H)-furanone as an oil consisting of only the cis isomer as observed by the <sup>1</sup>H NMR spectra and contaminated with less than 5% of starting material, which was not separable from the product: <sup>1</sup>H NMR (acetone-d<sub>6</sub>) δ 25

7.25-7.15 (m, 4H), 6.59 (d, 1H,  $J = 11.4$  Hz), 5.81-5.76 (m, 1H), 5.51-5.43 (m, 2H), 4.71 (dd, 1H,  $J = 3.5, 7.6$  Hz), 3.44-3.25 (m, 2H), 2.40-1.90 (m, 5H), 1.76-1.58 (m, 1H), 1.50-1.32 (m, 2H), 0.94 (t, 3H,  $J = 7.3$  Hz). Anal Calcd for  $C_{20}H_{24}O_4 + 0.25 H_2O$ : C, 71.20; H, 7.47. Found: C, 70.97; H, 7.32.

- 5 The following is a list of references related to the above disclosure. These references should be considered as incorporated by reference in their entirety.

1. Shimizu, T., et al. Enzyme with dual lipoxygenase activities catalyzes leukotriene A4 synthetase from arachidonic acid. Pro. Natl. Acad. Sci. 81:689-693, (1984).

2. Egan, RW and Gale PH, Inhibition of mammalian 5-lipoxygenase by aromatic disulfides, J. Biol. Chem. 260: 11554-11559, (1985).  
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3. Evans, AT, et al Actions of cannabis constituents on enzymes of arachidonic metabolism: anti-inflammatory potential. Biochem Pharm. 36:2035-2037, (1987).

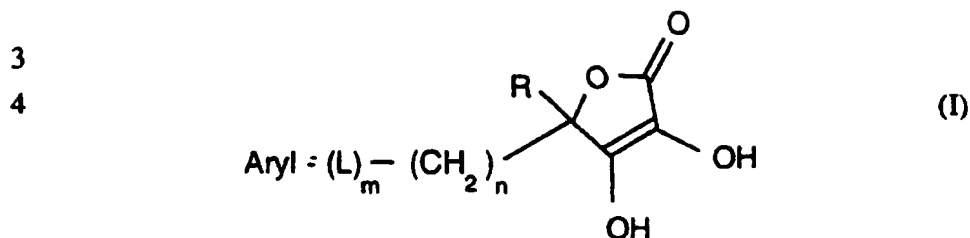
4. Boopathy, R and Baiasubramanian AS. Purification and characterization of sheep platelet cyclooxygenase. Biochem J. 239:371-377, (1968).

- 15 5. O'Sullivan, MG et al, Lipopolysaccharide induces prostaglandin H synthase-2 in alveolar macrophages. Biochem. Biophys. Res. Comm. 187: 1123-1127, (1992).

6. Mansuy D. et al, A new potent inhibitor of lipid peroxidation in vitro and in vivo, the hepatoprotective drug anisylthiolthione. Biochem. Biophys. Res. Comm. 135:1015-1021, (1986).

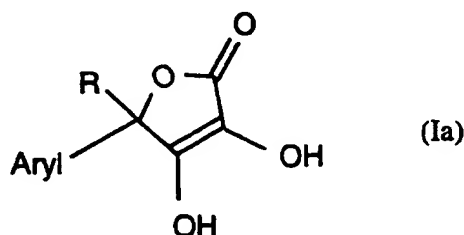
WHAT IS CLAIMED IS:

1 1. A compound of the formula I:



8 wherein R is hydrogen, phenyl, or a lower alkyl; L is a linker moiety selected from the  
9 group consisting of oxygen, sulfur, nitrogen, acetylene, a *cis* or *trans* carbon-carbon  
10 double bond, an ester, carbonate, urea, amide and carbamate; m is 0 or 1, n is 0 to 4,  
11 Aryl is a mono-substituted or unsubstituted aryl group; with the proviso that when R is  
12 hydrogen, then either m or n is not zero; or a pharmaceutically acceptable salt thereof.

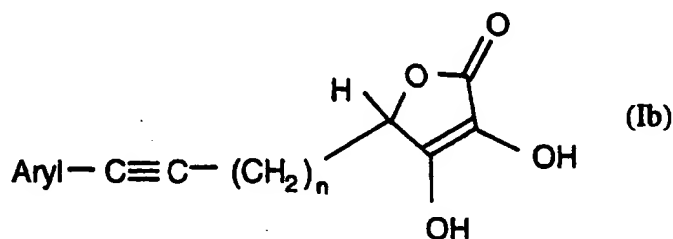
1 2. A compound according to Claim 1 of the formula Ia



8 wherein R is hydrogen, phenyl, or a lower alkyl; and Aryl is a mono-substituted or  
9 unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

1 3. A compound according to Claim 2 which is 5-[(1,1'-biphenyl)-4-yl]-3,4-  
2 dihydroxy-5-phenyl-2(5*H*)-furanone.

1 4. A compound according to Claim 1 of the formula Ib



8 wherein n is 0 to 4 and Aryl is a mono-substituted or unsubstituted aryl group; or a  
9 pharmaceutically acceptable salt thereof.

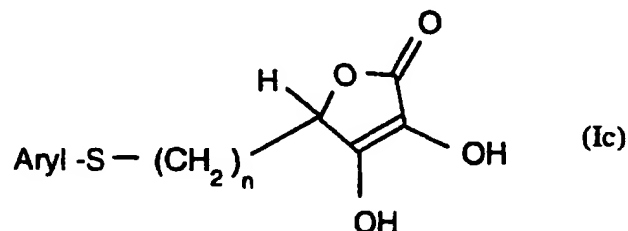
1 5. A compound according to Claim 4 which is 3,4-dihydroxy-5-[(4-(2-(2Z-  
2 hexenyl))phenyl)-3-butynyl]-2(5H)-furanone.

1 6. A compound according to Claim 4 which is  
2 3,4-dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5H)-furanone.

1 7. A compound according to Claim 4 which is  
2 3,4-dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5H)-furanone.

1 8. A compound according to Claim 4 which is  
2 3,4-dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5H)-  
3 furanone.

1 9. A compound according to Claim 1 of the formula Ic



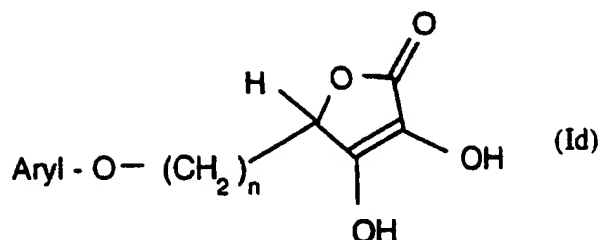
8 wherein n is 0 to 4 and Aryl is a mono-substituted or unsubstituted aryl group; or a  
9 pharmaceutically acceptable salt thereof.

1 10. A compound according to Claim 9 which is  
2 3,4-dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5H)-furanone.

1 11. A compound according to Claim 9 which is 3,4-dihydroxy-5-[2-(naphthyl-1-  
2 thio)ethyl]-2(5H)-furanone.

1 12. A compound according to Claim 9 which is 3,4-dihydroxy-5-[2-(naphthyl-2-  
2 thio)ethyl]-2(5H)-furanone.

1 13. A compound according to Claim 1 of the general formula Id



13 wherein n is 0 to 4 and Aryl is a mono-substituted or unsubstituted aryl group; or a  
14 pharmaceutically acceptable salt thereof.

1 14. A compound according to Claim 13 which is 3,4-dihydroxy-5-[2-(4-  
2 phenoxy)phenoxyethyl]-2(5H)-furanone.

1 15. A compound according to Claim 10 which is  
2 3,4-dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5H)-furanone.

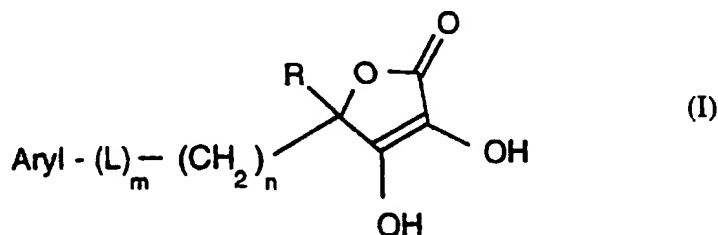
1 16. A compound according to Claim 10 which is  
2 5-[2-(dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5H)-furanone.

1 17. A compound according to Claim 10 which is  
2 3,4-dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5H)-furanone.

1 18. A compound according to Claim 10 which is  
2 3,4-dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5H)-furanone.

1 19. A compound according to Claim 10 which is  
2 5-[2-((1,1'-biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5H)-furanone.

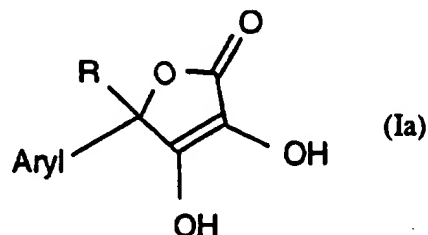
1 20. A pharmaceutical composition comprising an effective amount of a compound of the  
2 general formula I:



9 wherein R is hydrogen, phenyl, or a lower alkyl; L is a linker moiety selected from the  
10 group consisting of oxygen, sulfur, nitrogen, acetylene, a *cis* or *trans* carbon-carbon  
11 double bond, an ester, carbonate, urea, amide and carbamate; m is 0 or 1, n is 0 to 4,

- 12 Aryl is a substituted or unsubstituted aryl group; with the proviso that when R is  
 13 hydrogen, then either m or n is not zero; or a pharmaceutically acceptable salt thereof;  
 14 together with a pharmaceutically acceptable carrier therefor.

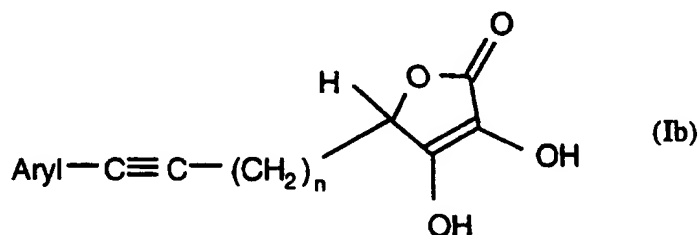
- 1 21. A composition according to Claim 20 of the formula Ia



- 8 wherein R is hydrogen, phenyl, or a lower alkyl; and Aryl is a substituted or  
 9 unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

- 1 22. A composition according to Claim 21 which is 5-[(1,1'-biphenyl)-4-yl]-3,4-  
 2 dihydroxy-5-phenyl-2(5*H*)-furanone.

- 1 23. A composition according to Claim 20 of the formula Ib



- 8 wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a  
 9 pharmaceutically acceptable salt thereof.

- 1 24. A composition according to Claim 23 which is 3,4-dihydroxy-5-[(4-(2-(2*Z*-  
 2 hexenyl))phenyl)-3-butynyl]-2(5*H*)-furanone.

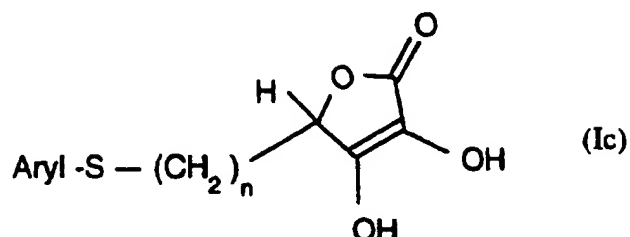
- 1 25. A composition according to Claim 23 which is  
 2 3,4-dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5*H*)-furanone.

- 1 26. A composition according to Claim 23 which is  
 2 3,4-dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5*H*)-furanone.

- 1 27. A composition according to Claim 23 which is  
 2 3,4-dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5*H*)-  
 3 furanone.



- 1 28. A composition according to Claim 20 of the formula Ic



- 8 wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a  
9 pharmaceutically acceptable salt thereof.

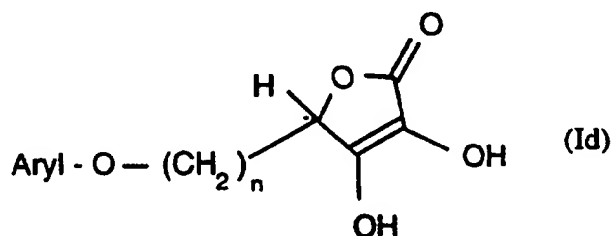
- 1 29. A composition according to Claim 28 which is

2 3,4-dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5H)-furanone.

- 1 30. A composition according to Claim 28 which is 3,4-dihydroxy-5-[2-(naphthyl-1-  
2 thio)ethyl]-2(5H)-furanone.

- 1 31. A composition according to Claim 28 which is 3,4-dihydroxy-5-[2-(naphthyl-2-  
2 thio)ethyl]-2(5H)-furanone.

- 1 32. A composition according to Claim 20 of the general formula Id



- 8 wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a  
9 pharmaceutically acceptable salt thereof.

- 1 33. A composition according to Claim 32 which is

2 3,4-dihydroxy-5-[2-(4-phenoxy)phenoxyethyl]-2(5H)-furanone.

- 1 34. A composition according to Claim 27 which is

2 3,4-dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5H)-furanone.

- 1 35. A composition according to Claim 27 which is

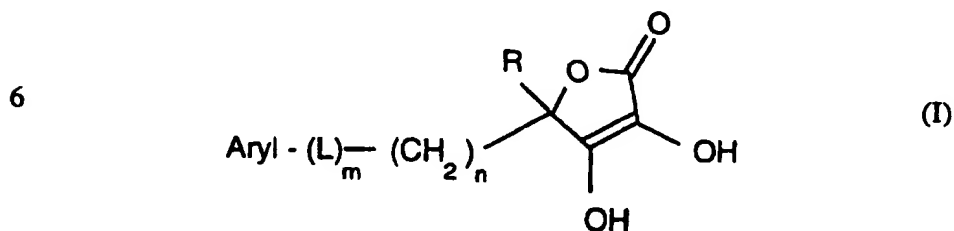
2 5-[2-(dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5H)-furanone.

- 1 36. A composition according to Claim 27 which is  
 2 3,4-dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5*H*)-furanone.

- 1 37. A composition according to Claim 27 which is  
 2 3,4-dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5*H*)-furanone.

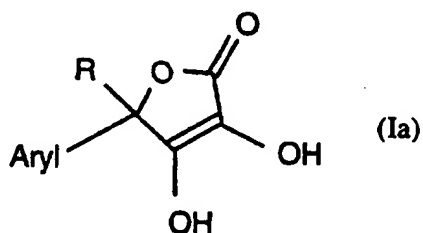
- 1 38. A composition according to Claim 27 which is  
 2 5-[2-((1,1'-biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone.

- 1 39. A method of treating a pathology involving acute or chronic inflammation which  
 2 comprises administration to a patient in need of such therapy an effective amount of a  
 3 compound of the formula



- 10 wherein R is hydrogen, phenyl, or a lower alkyl; L is a linker moiety selected from the  
 11 group consisting of oxygen, sulfur, nitrogen, acetylene, a *cis* or *trans* carbon-carbon  
 12 double bond, an ester, carbonate, urea, amide and carbamate; m is 0 or 1, n is 0 to 4,  
 13 Aryl is a substituted or unsubstituted aryl group; with the proviso that when R is  
 14 hydrogen, then either m or n is not zero; or a pharmaceutically acceptable salt thereof.

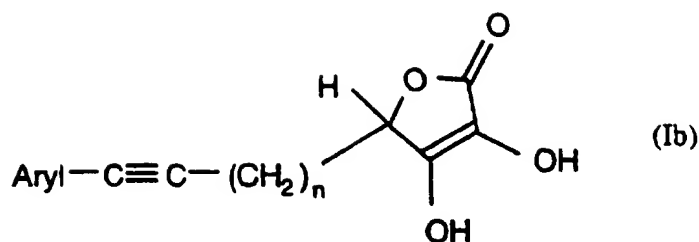
- 1 40. A method according to Claim 39 of the formula Ia



- 8 wherein R is hydrogen, phenyl, or a lower alkyl; and Aryl is a substituted or  
 9 unsubstituted aryl group; or a pharmaceutically acceptable salt thereof.

- 1 41. A method according to Claim 40 which is 5-[(1,1'-biphenyl)-4-yl]-3,4-  
 2 dihydroxy-5-phenyl-2(5*H*)-furanone.

- 1 42. A method according to Claim 39 of the formula Ib



9 wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a  
10 pharmaceutically acceptable salt thereof.

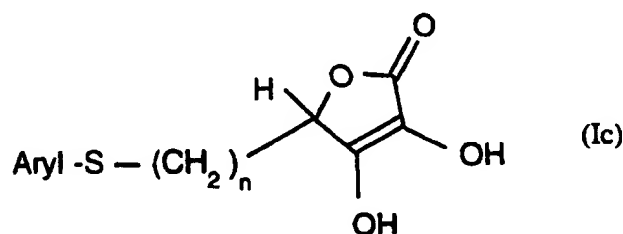
1 43. A method according to Claim 42 which is 3,4-dihydroxy-5-[(4-(2-(2Z-  
2 hexenyl))phenyl)-3-butynyl]-2(5H)-furanone.

1 44. A method according to Claim 42 which is  
2 3,4-dihydroxy-5-[(4-(2-(phenylthio)methyl)phenyl)-3-butynyl]-2(5H)-furanone.

1 45. A method according to Claim 42 which is  
2 3,4-dihydroxy-5-[4-(2-naphthyl)-3-butynyl]-2(5H)-furanone.

1 46. A method according to Claim 42 which is  
2 3,4-dihydroxy-5-[2-(4-(4-fluorophenylmethyl)thiophene)-(3-butynyl)]-2(5H)-  
3 furanone.

1 47. A method according to Claim 39 of the formula Ic



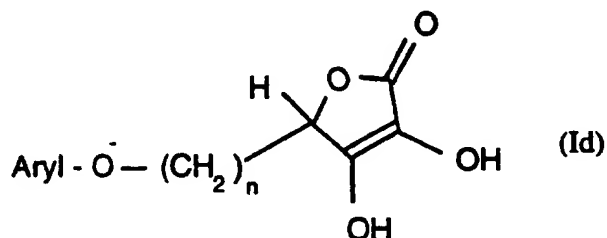
8 wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a  
9 pharmaceutically acceptable salt thereof.

1 48. A method according to Claim 47 which is  
2 3,4-dihydroxy-5-[2-(4,5-diphenyl-1,3-isoxazole-2-thio)ethyl]-2(5H)-furanone.

1 49. A method according to Claim 47 which is 3,4-dihydroxy-5-[2-(naphthyl-1-  
2 thio)ethyl]-2(5H)-furanone.

1 50. A method according to Claim 47 which is 3,4-dihydroxy-5-[2-(naphthyl-2-  
2 thio)ethyl]-2(5*H*)-furanone.

1 51. A method according to Claim 39 of the general formula Id



8 wherein n is 0 to 4, and Aryl is a substituted or unsubstituted aryl group; or a  
9 pharmaceutically acceptable salt thereof.

1 52. A method according to Claim 51 which is 3,4-dihydroxy-5-[2-(4-  
2 phenoxy)phenoxyethyl]-2(5*H*)-furanone.

1 53. A method according to Claim 48 which is  
2 3,4-dihydroxy-5-[2-(flavone-6-oxy)ethyl]-2(5*H*)-furanone.

1 54. A method according to Claim 48 which is  
2 5-[2-(dibenzofuran-2-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone.

1 55. A method according to Claim 48 which is  
2 3,4-dihydroxy-5-[2-(1-naphthoxy)ethyl]-2(5*H*)-furanone.

1 56. A method according to Claim 48 which is  
2 3,4-dihydroxy-5-[2-(diphenylmethane-2-oxy)ethyl]-2(5*H*)-furanone.

1 57. A compound according to Claim 48 which is  
2 5-[2-((1,1'-biphenyl)-4-oxy)ethyl]-3,4-dihydroxy-2(5*H*)-furanone.

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D307/62 A61K31/34 C07D307/91 C07D405/06 C07D417/06  
C07D405/12 C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 32194 A (UNIV OHIO STATE RES FOUND) 30 November 1995 see page 58 - page 61; claims; examples 7,8 see abstract	1-57
X	US 5 185 366 A (WITIAK DONALD T ET AL) 9 February 1993 see abstract; example 1 --- -/--	1,2

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"B" document member of the same patent family

Date of the actual completion of the international search

11 November 1997

Date of mailing of the international search report

21. 11. 97

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Authorized officer

Paisdor, B

## INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/US 97/14878

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 9211 Derwent Publications Ltd., London, GB; AN 92-085896 XP002046478 & JP 04 029 985 A (MEIJI SEIKA KAISHA) , 31 January 1992 see abstract & JP 04 029 985 A ---	1,20,39
A	A. T. HOPPER ET AL.: "Synthesis of Enantiomerically Pure Stereogenically Labile 4-Aryl-2-hydroxytetronic Acids from Enantiomerically Pure Silyl-Protected Mandelaldehydes: aci-Reductone Analogues of Propionic Acid Nonsteroidal Anti-inflammatory Agents" JOURNAL OF ORGANIC CHEMISTRY, vol. 60, 1995, EASTON US, pages 3334-3341, XP002046477 see page 3334, column 1 - page 3337, column 2 -----	1-57

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/ 14878

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 39-56  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.